Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Building capacity for active surveillance of vaccine adverse events in the Americas: A hospital-based multi-country network

Pamela Bravo-Alcántara [a], Silvia Pérez-Vilar [b,c,*], Helvert Felipe Molina-León [c], Miriam Sturkenboom [b,d], Steven Black [d,e], Patrick L.F. Zuber [f], Christine Maure [f], Jose Luis Castro [g], on behalf of the L.A.N.V.A.P. (Latin American Network for VAccine Pharmacovigilance) [1]

[a] Unit of Comprehensive Family Immunization, Department of Family, Gender and Life Course, Pan American Health Organization (PAHO/WHO), Washington DC, DC, United States
[b] Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands
[c] International Professional Consultant, Pan American Health Organization (PAHO/WHO), Washington DC, DC, United States
[d] Vaccine.GRID Foundation, Basel, Switzerland
[e] Department of Global Child Health, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States
[f] Department of Essential Medicines and Health Products, World Health Organization, Geneva, Switzerland
[g] Unit of Medicines and Health Technologies, Department of Health Systems and Services, Pan American Health Organization (PAHO/WHO), Washington DC, DC, United States

ARTICLE INFO

Article history:
Received 4 February 2017
Received in revised form 11 April 2017
Accepted 17 April 2017
Available online xxxx

Keywords:
Post-marketing surveillance
Vaccine safety
Global Vaccine Safety Initiative (GVSI)
Adverse events following immunization (AEFI)

ABSTRACT

New vaccines designed to prevent diseases endemic in low and middle-income countries are being introduced without prior utilization in countries with robust vaccine pharmacovigilance systems. Our aim was to build capacity for active surveillance of vaccine adverse events in the Americas. We describe the implementation of a proof-of-concept study for the feasibility of an international collaborative hospital-based active surveillance system for vaccine safety. The study was developed and implemented in 15 sentinel sites located in seven countries of the region of the Americas, under the umbrella of the World Health Organization (WHO) Global Vaccine Safety Initiative. The study evaluated the associations between measles-mumps-rubella vaccines and two well-recognized adverse events: Immune thrombocytopenic purpura (ITP) and aseptic meningitis. The regional network contributed 63 confirmed ITP and 16 confirmed aseptic meningitis eligible cases to the global study, representing, respectively, 33% and 19% of the total cases. To ensure long-term sustainability and usefulness to investigate adverse events following new vaccine introductions in low and middle-income countries, the network needs to be strengthened with additional sites and integrated into national health systems.

Abbreviations: AEFI, Adverse events following immunization; ICD, International Classification of Diseases; ITP, Immune thrombocytopenic purpura; LMIC, Low and middle-income countries; MMR, Measles-mumps-rubella; PAHO/WHO, Pan American Health Organization; SCCS, Self-controlled case series method; WHO, World Health Organisation.

* Corresponding author at: 10903 New Hampshire Ave, Silver Spring 20993, MD, United States.
E-mail address: silvia.perezvilar@fda.hhs.gov (S. Pérez-Vilar).

[1] L.A.N.V.A.P. (Latin American Network for VAccine Pharmacovigilance). **Argentina**: Vanesa E. Castellano (Hospital de Niños Ricardo Gutiérrez, Buenos Aires), Lucia Chiarvetti (Hospital José Bernardo Iturraspe, Santa Fé), Adriana Falcó (Hospital Público Materno Infantil, Salta, Mendoza), Angela Gentile (Hospital de Niños Ricardo Gutiérrez, Buenos Aires), Karina Guirau (Hospital Pediátrico Dr. Avelino L. Castelán, Ciudad de Resistencia), Maria Eugenia Pérez Carrega (Ministerio de Salud de la Nación, Buenos Aires), Susana Rasjido (Hospital Regional Teodoro J. Schestakow, Mendoza), Sofía Testino (H. Zonal Trelew Dr. Adolfo Margara, Trelew), Carla Vizzotti (Ministerio de Salud de la Nación, Buenos Aires). **Chile**: Marcela Avendaño (Ministerio de Salud, Santiago), Marcela González (H. Dr. Gustavo Fricke, Viña del Mar), Rosanna Lagos (Hospital de Niños Roberto del Río, Santiago), Marcelo Maturana (Hospital Clínico Regional Guillermo Grant Benavente, Concepción), Fernando Muñoz (Ministerio de Salud, Santiago), Adiela Saldaña (Instituto de Salud Pública, Santiago), Guillermo Soza (H. Regional de Temuco Dr. Hernán Henriquez Aravena, Temuco). **Colombia**: Martha Álvarez-Olmos (Fundación Cardioinfantil, Bogotá), Luz Amparo Sastoque (Instituto Nacional de Salud, Bogotá). **Costa Rica**: Marcela Hernández-de Mezerville (Hospital Nacional de Niños Dr. Carlos Sáenz Herrera, San José), Vicenta Machado (Caja Costarricense de Seguro Social, San José), Ileana Roverssi (Ministerio de Salud, San José), Angélica Vargas Camacho (Caja Costarricense de Seguro Social, San José). **Honduras**: Marco Tulio Luque (H. Escuela Universitaria, Tegucigalpa), Liset Mendoza (Ministerio de Salud, Tegucigalpa). **Perú**: Renne F. Aquije Hernández (Ministerio de Salud, Lima), Maria Esther Castillo Díaz (Instituto Nacional de Salud del Niño, Lima), Gladys Turpo Mamani (Centro Nacional de Epidemiología, Prevención y Control de Enfermedades, MINSA, Lima). **Uruguay**: Gustavo Giachetto, Noelia Speranza, Carlos Zunino (Centro Hospitalario Pereira Rossell, Montevideo).

http://dx.doi.org/10.1016/j.vaccine.2017.04.069
0264-410X/

1. Background

Low and middle-income countries (LMIC) are expected to become early users of new vaccines, without prior utilization in countries with robust vaccine pharmacovigilance systems. In many LMIC, the post-marketing surveillance capacity for vaccine safety and effectiveness is currently limited and needs to be strengthened [1–3]. Therefore, LMIC, particularly those that both manufacture and use prequalified vaccines, should have an expanded vaccine pharmacovigilance capacity that includes the use of stimulated and active surveillance, and the ability to perform population-based studies and epidemiological studies for hypothesis testing, when appropriate [4,5]. However, on their own, most LMIC do not have the technical capacity and/or do not have large enough populations under adequate surveillance to evaluate rare serious adverse events [4]. A sustainable collaborative international framework, using existing resources and infrastructures, could strengthen the current post-licensure pharmacovigilance systems [1,6]. Because of the primary interest on rare adverse events following immunization (AEFI) and limited resources, case-only methods are an attractive alternative for use in LMIC. [7–12].

The Global Vaccine Safety Initiative is a WHO forum for implementation of the Global Vaccine Safety Blueprint, which is a strategic framework reference document that aims to optimize the safety of vaccines through effective use of pharmacovigilance principles and methods [2,5,13]. In this context, a proof-of-concept study for the feasibility, data quality, and sustainability of an international collaborative hospital-based active surveillance system for vaccine safety was developed and implemented in sentinel sites from the six WHO regions, including the region of the Americas. For this proof-of-concept project, it was important to select: (a) a vaccine recommended in most participating countries, (b) one or more adverse events know to be associated with, at least, some of the vaccine strains in current use in those countries, and (c) adverse events that, at least in severe cases, would require hospitalization.

Initial expressions of interest were sought through WHO regional offices, during a WHO-sponsored meeting in Bangkok, Thailand, in June 2013, and during a PAHO/WHO-sponsored meeting in Barranquilla, Colombia, in November 2013. Country national teams, PAHO/WHO secretariat, and the coordination team agreed to use measles-containing vaccines as the test vaccine, and both immune thrombocytopenic purpura (ITP) and aseptic meningitis as the adverse events of interest for the WHO international proof-of-concept hospital-based active surveillance system, using case-only methods. Our aim was to start building capacity for active surveillance of vaccine adverse events in the Americas.

2. Methods

2.1. Site selection and capability assessment in the Americas

PAHO/WHO selected the participating sites for this proof-of-concept study based on: (a) commitment to participate, (b) regionally balanced representation, (c) capacity of the institution in terms of catchment area, (d) capacity of the institution in terms of database system availability, (e) diagnosis coding system used, (f) access to immunization records, (g) capacity of linkage between outcomes and exposures, (h) previous experience with post-marketing vaccine safety surveillance, (i) ability to access individual laboratory data, and (j) ability to review patient medical records, including availability of a physician or nurse for data collection. Ministries of Health were responsible for recruitment and coordination of participating hospitals.

Based on decisions taken at the PAHO/WHO-sponsored meeting in Barranquilla, the Americas selected sites to participate in a simulation surveillance exercise, in order to determine their actual capacity to identify potential cases discharged from the hospital with a pre-specified test diagnosis (pyelonephritis), determine availability of appropriate vaccination records for the vaccine (measles-mumps-rubella (MMR) vaccine) investigated, as well as capacity of linkage between outcome and exposure. This exercise also allowed PAHO/WHO to assess the sites' capacity to collect high quality data and evaluate the resources needed to conduct such investigations.

2.2. Regional adaptations of the proof-of-concept protocol and local Ethics Committee's approvals

Regional adaptations to the protocol were agreed upon during the first face-to-face PAHO/WHO-sponsored investigator meeting in Santiago, Chile, in June 2014. During this meeting, additional search criteria were added to identify potential cases through the hospital discharge databases in order to fit with current clinical practices in the region. Since the option of a common protocol for the whole project was chosen [14], additional cases identified using PAHO's criteria (see supplementary materials) were included only as a sub-analysis for the region.

The proof-of-concept study consisted of an international retrospective observational study to evaluate the association between ITP and aseptic meningitis and the administration of the first dose of MMR vaccines. The study included all ITP and aseptic meningitis cases hospitalized in any of the selected sites between January 2010 and March 2014. Study methods, including case definitions for both ITP and aseptic meningitis, are described elsewhere [30]. The protocol was approved by all local and WHO Ethics Committees, which provided a waiver of informed consent according to the article 32 of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). Given the need for accurate information on vaccination status, a waiver to contact parents or legal representatives in case of lack of information was also obtained.

2.3. Proof-of-concept implementation in the Americas

Prior to start of data collection, a second face-to-face PAHO/WHO-sponsored investigator meeting was organized in March 2015 in Santiago, Chile, with attendance from all participating sites. Following this meeting and the performance of a distance learning exercise to test data collection and quality using dummy cases, several sites helped identify issues in the Manual of Procedures that needed further clarification.

Data collection started in June 2015 and all countries submitted the de-identified data by December 2015. Using standardized procedures, the global coordination team reviewed the data submitted and sent a report to all sites detailing inconsistencies and missing data found. Sites were asked to submit final data for analysis, which was completed by the end of 2016. Operating procedures for data collection, data entry, and data submission for the global study are shown in Fig. 1.

2.4. Data quality assurance in the Americas

The proof-of-concept study was based on the evaluation of two well-established relationships, the risk of ITP and aseptic meningitis following first dose of MMR vaccines [15–20], since the project was focused on ensuring and testing data quality. Thus, a quality assurance plan was designed in parallel with the master study protocol and the Manual of Procedures.

PAHO/WHO made additional efforts to ensure a standardized data collection, by closely supporting the sites with algorithms needed to extract probable cases from their hospital discharge

Please cite this article in press as: Bravo-Alcántara P et al. Building capacity for active surveillance of vaccine adverse events in the Americas: A hospital-based multi-country network. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.04.069