Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Value of an in-depth analysis of unpublished data on the safety of influenza vaccines in pregnant women

Neal A. Halsey *, Tina Proveaux

Institute for Vaccine Safety, Department of International Health, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, w5041, Baltimore, MD, USA

ARTICLE INFO

Article history:
Received 15 August 2017
Received in revised form 14 September 2017
Accepted 15 September 2017
Available online xxxx

Keywords:
Influenza vaccine
Pregnancy
Vaccine safety

ABSTRACT

Background: Unpublished data can sometimes provide valuable information on the safety of biologic products.
Methods: We assessed information potentially available from regulatory authorities, manufacturers, and public health agencies. We explored 4 recently established vaccine registries, reviewed package inserts from 99 influenza vaccines, and contacted vaccine manufacturers and regulatory agencies for data on influenza vaccine safety in pregnant women.
Results: The vaccine registries did not have sufficient data to analyze and there are problems with the quality of the information. The majority of package inserts provided no product-specific safety information for pregnant women, especially in less developed countries. The majority of available data come from reports gathered from passive adverse event reporting systems in the general population and reports of women enrolled in clinical trials of influenza vaccines who became pregnant at various times before or after receiving influenza vaccine. The information was not collected in a systematic manner, there are inconsistencies in the follow up of pregnant women and the available information about pregnancy outcomes. Considerable resources would be needed to systematically identify all of the information, try to obtain missing follow up information, and conduct analyses. There would be substantial limitations to any attempt to conduct a systematic analysis.
Conclusions: The value of trying to analyze unpublished data on the safety of influenza vaccine in pregnancy is limited and would require considerable resources to thoroughly investigate. Expanding efforts to identify and review unpublished data regarding the safety of influenza vaccines in pregnancy is not likely to produce information of high scientific value or information that could not be identified from publications and other publically available data.

1. Introduction

The World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) has recommended maternal influenza immunization [1]. As part of the overall effort WHO requested a review of the potential value of conducting an in-depth analysis of unpublished data on the safety of influenza vaccine during pregnancy.

2. Methods

We conducted online searches to identify public datasets and accessed potential sources of unpublished data from vaccine manufacturers, online package inserts, regulatory agencies, and online clinical trials databases for information relevant to the safety of influenza vaccines during pregnancy (Table 1). We also contacted some key individuals responsible for this information for assistance.

The European Medicines Agency (EMA) provided information to us dated May 19, 2015 about all the manufacturers that had obtained central approval via the EMA. The Documents Manager conducted several searches for us and abstracted the data available (Appendix 1). There was no specific data provided in the database they sent, but study numbers within the database could be used to conduct a search on the EMA site to find specific study data and results. We also searched for information on the EMA website.

The US Food and Drug Administration (FDA) maintains a website with information on licensed vaccines. The information available on the section "Vaccines Licensed for Use in the United States" lists product names and trade names and links to documentation regarding product approval, new indications and package

* Corresponding author.
E-mail address: nhalsey1@jhu.edu (N.A. Halsey).

https://doi.org/10.1016/j.vaccine.2017.09.049
0264-410X/

Table 1
Sources and URLs.

Organization		Source	URL/Website
	Collaboration: Astellas, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Eisai, GSK, Lilly, Novartis, Roche, Sanofi, Takeda, UCB and ViiV Healthcare	Clinical Study Data Request	clinicalstudydatarequest.com
EMA	European Medicines Agency		www.ema.europa.eu/ema
EU	European Union	EudraCT – EU Clinical Trails Register	www.clinicaltrialsregister.eu/ctr-search/search
FDA	(US) Food and Drug Administration	Vaccines Licensed for Use in the United States	www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm
FDA	(US) Food and Drug Administration	Postmarketing Requirements	www.accessdata.fda.gov/scripts/cder/pmc/index.cfm
FDA/CDC	(US) Food and Drug Administration and (US) Centers for Disease Control and Prevention	VAERS – Vaccine Adverse Event Reporting System	vaers.hhs.gov/
NIH	(US) National Institutes of Health	Clinical Trials	www.clinicaltrials.gov
WHO	World Health Organization	International Clinical Trials Registry Platform	apps.who.int/trialsearch

inserts. A manufacturer submitting a Biologic License Application (after finishing the 3 phases of clinical development) must submit safety and efficacy data available for the product, including published and unpublished studies. A summary of postmarketing requirements is available online.

Vaccine manufacturers: In 2015, we identified 47 manufacturers of 91 influenza vaccines distributed in the EU and the US, Canada, Australia, New Zealand, Taiwan, India, China with information available online [2], this information was updated to include more recent information on a total of 99 influenza vaccines. All 99 of these package labels/inserts were available online and were reviewed for relevant information.

2.1. Clinical trials data

Clinicaltrials.gov is a registry and database of clinical studies conducted in human subjects throughout the world (190 countries) maintained by the US National Institutes of Health. Conducting an Advanced Search using Other Terms: 'influenza vaccine NOT Haemophilus NOT Hib", Conditions: 'pregnant OR pregnancy OR maternal'.

EU Clinical Trials Register (EudraCT) is a database of clinical trials within the European Economic Area (EEA). Trials with sites outside the EEA are included if they are "marketing authorisation holder-sponsored and involve the use in the paediatric population of a medicinal product covered by an EU marketing authorisation ... or if they form part of an agreed PIP (Paediatric Investigation Plan)". This registry includes pediatric clinical trials and Phase II-IV adult clinical trials.

WHO International Clinical Trials Registry Platform (ICTRP) is a registry containing ongoing and completed clinical trials. This searchable site contains trial data sets around the world. The ICTRP was searched for trials using Advanced Search with the following parameters – Title: "influenza vaccine" AND Condition: "pregnant OR pregnancy OR maternal", NOT Intervention: "Haemophilus" and setting Recruitment status to ALL (the default is "Recruiting").

Clinical Study Data Request includes studies from sponsors who have stated commitments to use this open access site. A search of the Clinical Study Data Request site was conducted in July 2017 with the following parameters: Search all Sponsors, Find by: Medicine = Influenza Vaccine (there was an option for Medical Condition but nothing to indicate pregnancy). This site did not allow for an Advanced Search.

The US Centers for Disease Control and Prevention (CDC): The Immunization Safety Office coordinates assessments of individual adverse events, post-licensure clinical trials, and epidemiologic investigations of safety for vaccines marketed in the United States. Unpublished data from these investigations are sometimes presented at meetings of the Advisory Committee on Immunization Practices (ACIP) which makes recommendations for the use of vaccines in the United States. We monitored ACIP meetings via webcast and searched the CDC website for additional information. Investigators at the CDC periodically present unpublished data at ACIP meetings.

2.2. Vaccine Adverse Event Reporting System (VAERS) and other passive reporting systems

The CDC and the FDA maintain the **Vaccine Adverse Events Reporting System (VAERS)** a national post-marketing vaccine safety surveillance program of reported adverse events following immunizations administered primarily in the United States. Reports are accepted for vaccines administered in other countries, but analyses are done primarily for data obtained from the United States. Other countries and the European Union have separate databases similar to VAERS.

3. Results

The EMA requires manufacturers to conduct post licensure safety studies and requires manufacturers to provide risk management plans (RMPs) to address theoretical concerns about safety in pregnant women for some influenza vaccines. Consulting with the Documents Manager or searching through their database was time-consuming and inefficient.

A search of the FDA's database on the Postmarket Requirements and Commitments page on August 3, 2017 (www.accessdata.fda.gov/scripts/cder/pmc/index.cfm) using only the parameter "Product: influenza vaccine" resulted in 13 Applications/Supplements. Of the 6 applications relevant to pregnancy registries 3 are ongoing and 3 are pending; none had data posted.

Some of the influenza vaccine manufacturers with the highest sales revenue in 2015 are listed in (Table 2). The package labeling/inserts provided by manufactures for most influenza vaccines contains wording about use of the product in pregnant women; however, much of the information is vague, cites animal studies or general information not specific to the product. The wording in the package inserts regarding use of the vaccines in pregnancy varies considerably ranging from "...no evidence of harm..." to "...forbidden to use..." As noted by Regan [3], this information contradicts the clear recommendations for the use of influenza vaccine in pregnant women and adds to confusion of providers and consequently leads to lower rates of maternal vaccination.

Seasonal influenza vaccine was recommended for use during pregnancy in 29% of the identified package inserts; 44% recommended use with a caveat (ie, 'if clearly needed', 'if benefits out-