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Reference set for performance testing of pediatric vaccine safety signal detection methods and systems

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ABSTRACT

Background: Safety signal detection in spontaneous reporting system databases and electronic healthcare records is key to detection of previously unknown adverse events following immunization. Various statistical methods for signal detection in these different datasources have been developed, however none are geared to the pediatric population and none specifically to vaccines. A reference set comprising pediatric vaccine-adverse event pairs is required for reliable performance testing of statistical methods within and across data sources.

Methods: The study was conducted within the context of the Global Research in Paediatrics (GRiP) project, as part of the seventh framework programme (FP7) of the European Commission. Criteria for the selection of vaccines considered in the reference set were routine and global use in the pediatric population. Adverse events were primarily selected based on importance. Outcome based systematic literature searches were performed for all identified vaccine-adverse event pairs and complemented by expert committee reports, evidence based decision support systems (e.g. Micromedex), and summaries of product characteristics. Classification into positive (PC) and negative control (NC) pairs was performed by two independent reviewers according to a pre-defined algorithm and discussed for consensus in case of disagreement.

Results: We selected 13 vaccines and 14 adverse events to be included in the reference set. From a total of 182 vaccine-adverse event pairs, we classified 18 as PC, 113 as NC and 51 as unclassifiable. Most classifications (91) were based on literature review, 45 were based on expert committee reports, and for 46 vaccine-adverse event pairs, an underlying pathomechanism was not plausible classifying the association as NC.

Conclusion: A reference set of vaccine-adverse event pairs was developed. We propose its use for comparing signal detection methods and systems in the pediatric population.

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1. Introduction

Every year, more infants, children, and adolescents are protected from illness, disability and death by virtue of global immunization programs [1,2]. Robust systems for monitoring benefits and risks of these programs and the vaccines administered are pivotal for program sustainability, the safety of the mostly healthy vaccine recipients and for maintaining public confidence in the vaccine [3,4]. This requires the ability to reliably detect safety signals in the pediatric population in a globally harmonized approach.

Today, various definitions of what constitutes a signal exist including definitions by WHO and CIOMS. The latter defined safety signal as follows: 'Information that arises from one or multiple sources (including observations and experiments) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action' [5,6]. Further, various

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methods for signal detection in spontaneous reporting system (SRS) databases and electronic healthcare records (EHR) have been developed for drugs [7]. Approaches to test their performance within systems and to compare systems are based on reference sets comprising drug/vaccine-adverse event pairs with a high likelihood for a strong association (positive controls [PC]) and an absence of any association (negative controls [NC]). A reference set allows assessing if statistical methods can detect expected positive or no associations between events and vaccines. Previous approaches to develop such standards for drugs included consulting reference books such as the Physicians Drug Reference or Martindale [8], considering label changes [9], combining information from summary of product characteristics (SPC) and the literature as in two recent initiatives, the 'Observational Medical Outcomes Partnership (OMOP)' and the 'EU-ADR project' [10,11]. Work on validating approaches for the pediatric population is in progress [12].

However, to the best of our knowledge no such reference sets are available for vaccines. The aim of the current study was to develop such a reference set applicable in SRS databases and EHR around the globe to test performance of statistical methods for signal detection and the systems in general.

2. Methods

The study was conducted within the context of the Global Research in Paediatrics (GRiP) project, funded under the seventh framework programme (FP7) of the European Commission. FP7 is a funding program of the European Union for Research and Innovation. The main goal of GRiP is to establish a network of excellence to improve the development and safe use of medicines in children (www.grip-network.org).

2.1. Selection of vaccines

As the GRiP project focuses on the performance testing of statistical methods for signal detection of pediatric vaccines, we only considered vaccines which are used in children for the construction of the reference set. Vaccines also had to be routinely used for several years to ascertain adequate exposure and to allow detection of associations with potentially rare adverse events of interest. As GRiP is an international project, most of the included vaccines should also have global utility and applicability. These criteria resulted in the inclusion of 13 commonly used vaccines: Bacillus Calmette–Guérin (BCG), diphtheria-tetanus-acellular pertussis (DTaP), diphtheria-tetanus-whole cell pertussis (DTPw), hepatitis A (HAV), hepatitis B (HBV), haemophilus influenzae type B (Hib), influenza (any type), pneumococcal (PV), meningococcal (MV), measles-mumps-rubella (MMR), oral polio (OPV), rotavirus (RV) and varicella zoster virus (VZV) vaccine.

2.2. Selection of adverse events

Given the expectation that few PCs might be found, adverse events were first selected based on their likelihood of being PCs for at least one vaccine based on literature review or their previous formal evaluation in an official report. The list was then narrowed down based on the specificity and importance of the event [13]. Thus, we selected clearly defined clinical entities to increase the likelihood of comprehensive literature searches and comparable data sets for performance testing. Adverse events generally considered to be "important" in the European and North American routine immunization programs were prioritized, because their reporting is generally required in most member states of these regions regardless of the available knowledge on their causal association with specific vaccines. A total of 14 adverse events were included: anaphylaxis, arthritis, Bell's palsy, convulsions, insulin-dependent diabetes mellitus (IDDM), disseminated BCG-itis, encephalitis, disseminated Oka VZV, Guillain-Barré Syndrome (GBS), hypotonic hyporesponsive episode (HHE), intussusception, thrombocytopenia, vaccine-associated paralytic poliomyelitis (VAPP), and wheezing (reactive airway disease). This resulted in a total of 182 vaccine-adverse event pairs which needed to be classified into PC or NC, or unclassifiable [UC].

Table 1
Search algorithm for Bell's palsy as an adverse event following immunization – an example.

Medline	#1 exp Vaccines/(Mesh)
	#2 exp Vaccination/(Mesh)
	#3 exp Immunization/(Mesh)
	#4 (vaccin$ OR immuni$ OR inoculat$).tw.
	#5 or/1–4
	#6 exp Bell Palsy/(Mesh)
	#7 exp Facial Paralysis/(Mesh)
	#8 (bell$ palsy OR facial$ paralys$ OR facial diplegia OR facial nerve paralys$ OR facial nerve palsy OR facial nerve paresis OR facial palsy OR facial paresis OR prosopoplegia OR facioplegia OR facial weakness OR facial synkinesis OR facial neuropath$).tw.
	#9 ((seventh cranial nerve OR 7th cranial nerve) adj (palsy OR paralys$ OR paresis OR neuropath$)).tw.
	#10 ((seventh nerve OR 7th nerve) adj (palsy OR paralys$ OR paresis OR neuropath$)).tw.
	#11 (face adj (paralys$ OR palsy OR paresis OR neuropath$)).tw.
	#12 or/6–11
	#13 5 and 12
	#14 limit 13 to (english language and humans)

2.3. Literature search and included studies

We performed literature searches until end of 2012 in MedLine through OvidSP (from 1946), Embase (all years) and the Cochrane Library and extracted the references to EndnoteX7. Table 1 exemplifies a search algorithm in Medline. All other search strategies are available from the authors on request. To maximize the number of potentially relevant studies, we performed the searches by outcome instead of specific searches by vaccine-event pair. An exception was made for anaphylaxis, where we performed a specific vaccine-event pair search for unknown associations (i.e. associations between anaphylaxis and OPV, RV, Hib, BCG and PV) to reduce the size of the highly sensitive search result. We focused on English literature with no age restrictions and reviewed the search result of vaccine-event pairs that were not previously reviewed and classified by the Institute of Medicine (IOM, 2011 report on 'Adverse effects of vaccines – Evidence and Causality', 2004 report on 'Influenza Vaccines and neurological complications') [13,14], or included in WHO information sheets [15] or in the Vaccine Injury Table (VIT) [16] (91 in total). For each vaccine-event pair of interest, we included all relevant studies by title or abstract in the first instance, and by full text, if the title or abstract did not provide sufficient information. As in the IOM report, review papers, letters and editorials were not included. However, we checked these publications for any additional relevant references of original data.

We extracted study identifiers (author, title, publication year), details on type of study, vaccine of interest, sample size, age category of the study population, number of cases with the adverse event of interest and risk measure(s) by using a standard data extraction form (available from the authors upon request). A first extraction of relevant articles was performed individually by CN, MP and YB. Subsequent classification of vaccine-adverse event pairs based on the extracted literature (described below) was done by two reviewers (from the list of authors) in parallel and then discussed for consensus with a third arbitrator (JB or TV) in case of uncertainties. The quality of the extraction process of relevant articles was randomly double-checked.

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