HEALTH PROMOTION

Active surveillance of adverse events after immunization (AEFI) from the Local Health Unitof Ferrara, Italy

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Keywords

Vaccination • Adverse events after immunization • Surveillance system • Vaccine vigilance

Summary

Introduction. *Vaccine vigilance implies the collection, evaluation, analysis and communication of adverse events following immunization (AEFI) and is a useful tool for vaccine monitoring allowing, even after approval and marketing, to check its safety/tolerability. The multiregional project "Active surveillance of adverse vaccine reactions", joined by the AUSL of Ferrara, is aimed at making parents of children, who have undergone at least one vaccination provided by the regional vaccination calendar in the first 24 months of life, aware of the reporting of any AEFI via mobile phone-SMS.*
Methods. *An analysis of the project data, collected in the period March 2018 - May 2019, was carried out, to evaluate the effectiveness of the reporting tool and the type and frequency of AEFI. Anonymized data were analyzed by number, gender, distribution by age, type of vaccine, adverse event, severity and outcome.*
Results. *A total of 1,494 consents and 983 SMS messages were obtained from parents. The vaccine doses carried out were 1,984 (28.3% hexavalent, 28% PCV13, 17% anti-rotavirus, 14.3% Men-B). Almost all (99.5%) AEFI were classified as "not serious". Based on the Organ System Class (SOC), most reports are related to "General Disorders and Administration Site Conditions" (52.3%), followed by "Psychiatric Disorders" (26.5%) and "Metabolic and nutrition disorders" (12.5%).*
Conclusions. *The reported AEFI are in line with the ones reported in the literature. Reporting via SMS is a valid vaccine surveillance tool contributing to the qualitative and quantitative improvement of the information transmitted.*

Introduction

In recent years, the safety of vaccines has aroused particular interest, also following the important changes in the management of vaccinations introduced with law no. 119 of 31 July 2017 [1]. In this context, vaccine vigilance is configured as a tool of fundamental importance to deepen knowledge on the safety of vaccines [2]. Vaccine vigilance is the set of pharmacovigilance activities related to the collection, evaluation, analysis and communication of adverse events following immunization.
An adverse event following a vaccination (Adverse Events Following Immunization, AEFI) is defined as "any adverse clinical event that occurs after the administration of a vaccine and which does not necessarily have a causal relationship to it. The adverse event could be an unfavorable or unintended sign, an abnormal laboratory result, a symptom or a disease" [3].
The only relation between the carried-out vaccination and the harmful event could be the temporal one, considering that the greater the interval between vaccination and the event, the lower the plausibility of a possible causal link between the two [3].
Vaccine vigilance therefore has the dual purpose of guaranteeing the safety of the vaccination act and keeping up to date the evaluation of the risk/benefit ratio, verifying that the latter remains favorable over time, especially in consideration of the fact that vaccination is offered to a healthy population [4].
Monitoring is mainly carried out through two methods: passive vaccine vigilance, that is the spontaneous reporting of adverse events following vaccination, and active one, which is stimulated reporting through independent studies.
In particular, active vaccine surveillance consists in the monitoring and evaluation of reports of suspected adverse reactions to vaccines performed by healthcare professionals or particular categories of users in specific situations stimulated by appropriate independent studies; these studies are conducted by the Regions in collaboration with the Italian Medicines Agency (AIFA) and other international regulatory bodies [5].
Since the main limitation of spontaneous reporting is represented by under-reporting, i.e. the failure to report

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Tab. I. Pediatric vaccination calendar of the Emilia-Romagna Region, in force since 1 January 2018.

Calendar	0-30 days	3rd month	4th month	5th month	6th month	7th month	11th month	13th month	14th month	6 years	12th month	13-14 years
DTaP		x		x			x			x		x
IPV		x		x			x			x		x
HBV	x *	x		x			x					
HiB		x		x			x					
MMR								x		x		
V**								x		x		x °
PCV		x		x			x					
Men B			x		x	x			x			
Men ACWY								x				x
RV		x		x								
HPV											x	
Flu§												

Vaccines: DTaP: diphtheria, tetanus and acellular pertussis; IPV: inactivated poliovirus; HBV: hepatitis B; HiB: *Haemophilus influenzae* type b; MMR: measles, mumps and rubella; V: varicella; PCV: conjugate pneumococcal; Men B: meningoccal B; Men ACWY: quadrivalent conjugate meningococcal; RV: rotavirus; HPV: human papillomavirus; Flu: influenza.
* Newborns from HBsAg positive mother. ** Newborns since 2017. ° 2 doses provided to susceptible subjects. § Starting from 6th month, only for at risk children.

Tab. II. Pediatric vaccination calendar of the Emilia-Romagna Region, in force since 1 January 2019.

Calendar	0-30 days	3rd month	4th month	5th month	6th month	7th month	11th month	13th month	14th month	6 years	12th month	13-14 years
DTaP		x		x			x			x		x
IPV		x		x			x			x		x
HBV	x *	x		x			x					
HiB		x		x			x					
MMR								x		x		
V**								x		x		x °
PCV		x		x			x					
Men B			x		x				x			
Men ACWY								x				x
RV		x	x	x								
HPV											x °°	
Flu§												

Vaccines: DTaP: diphtheria, tetanus and acellular pertussis; IPV: inactivated poliovirus; HBV: hepatitis B; HiB: *Haemophilus influenzae* type b; MMR: measles, mumps and rubella; V: varicella; PCV: conjugate pneumococcal; Men B: meningoccal B; Men ACWY: quadrivalent conjugate meningococcal; RV: rotavirus; HPV: human papillomavirus; Flu: influenza.
* Newborns from HBsAg positive mother. ** Newborns since 2017. ° 2 doses provided to susceptible subjects. °° 2 doses (6 months of interval between doses). § Starting from 6th month, only for at risk children

a certain number of adverse reactions that hinders an estimation of the real incidence of adverse events, it is desirable to promote active vaccine surveillance programs in order to increase the awareness of patients and healthcare professionals to the issue of vaccine safety [6, 7].

In 2017, the Local Health Unit of Ferrara, Italy, together with the Provincial Center for Pharmaco-vigilance, joined the multiregional project "Reporting of adverse events after vaccination by parents", promoted by the Veneto Region, which also involved other regions as Sicily, Marche, Calabria, Piedmont and the Autonomous Province of Bolzano.

The context in which the project is inserted, looks at a national data with most of the reports related to immunization from health districts (which remain a very important point in the observation of adverse events) especially in the first two years of life, a period in which, according to the national vaccination calendar, immunization sessions are fairly close in time.

The proposed primary objective of this intervention is to increase the reporting rate of adverse events after immunization. Another goal of primary importance, but more difficult to quantify, is the involvement of citizens (parents) in the reporting of adverse events after immunization.

The tool to pursue this objective has been identified in the use of the SMS (short message service) mobile phone system in order to facilitate the adhesion of parents and, at the same time, to reduce the workload of health professionals in filling out the reporting.

The secondary objective is to speed up the management of reports by Pharmaco-vigilance Managers and to improve the collection of reports and the organization of the vaccine vigilance system, through the use of the *VigiFarmacoVax* platform.

Tab. III. Specific adverse events following immunization (AEFI).

Specific AEFIs	(n[1])	(%)
Pyrexia	468	37.5
Mood disorders	331	26.5
Gastrointestinal disorders	156	12.5
Local disturbances	116	9.3
Sleep disturbances	104	8.3
Crying	38	3.0
General malaise, asthenia, weakness, sweating	17	1.4
Hyperpyrexia	14	1.1
Upper respiratory tract infection, pneumonia, acute otitis	3	0.2
Seizures, ocular congestion	1	0.1

[1] The sum of the values does not equal the total of the AEFI.

Methods

The project "Reporting of adverse events after vaccination by parents", to which the Local Health Unit of Ferrara has joined with the participation of the Community Pediatrics of the central-northern district, took place over 15 months, from March 2018 to May 2019, preceded by a pilot phase in May 2017.

The study population was represented by all children aged ≤ 2 years who underwent a vaccination according to the regional vaccination calendar in the period March 2018 - May 2019 (Tabs. I, II).

During each vaccination session, after having explained to the parents the methods and purposes of the active vaccine surveillance project, they were given the information letter, shared with the coordinating center and the pediatricians of the vaccination center, and the informed consent to participate in the study, in which, they were also asked to indicate a mobile number, in order to be subsequently contacted via SMS. Data gathering was conducted following the principles of the Declaration of Helsinki, according to current national legislation and in compliance with the protection of personal data. All data were anonimyzed.

Within 7 or 21 days from the vaccination session, depending on the type of administered vaccine (inactivated or live attenuated vaccine), an SMS was sent to the parent asking for the description of any adverse events occurring in the days after vaccination - "Did any adverse events occur after the vaccine administered on dd/mm/yy? If yes, please describe them by indicating the date of onset of symptoms. Thanks, the District".

The tools used included an informatic platform, *VigiFarmacoVax*, and a mobile phone system. *VigiFarmacoVax* is a specific software platform that allows the collection of data of vaccinated children (name, surname, sex, date of birth, vaccination clinic, vaccination date, type of vaccine and mobile phone number) and the automatic sending of the message to the parent who joined the project; even the return information, received via SMS from the parents, is managed by the same platform.

The parent can respond to the message without a time limit from receiving the same and the response, in the case of vaccinations performed at different times, was always attributed to the last vaccine administered. The text of the message was controlled by the platform through an algorithm that makes it possible to recognize the messages that describe adverse events and if these are to be considered serious. This recognition occurred by searching for the terms contained in a list of clinical events considered serious (IME LIST). If the text of the message contained one or more of these terms, then the system inserted an alert symbol next to the text of the message and placed this alert at the top of the list, awaiting confirmation from healthcare professionals.

All reports, to be sent to the *VigiFarmacoVax* platform, must be validated; validation requires the presence in the message of at least one adverse event and the assessment of the seriousness proposed by the system, also allowing the inclusion of additional information in the "comments of the reporter". Following validation, the messages were classified into 3 classes:

- messages without adverse events;
- messages with adverse events not reported in *VigiFarmacoVax* (discarded, that is, the message is saved and archived, without sending data to *VigiFarmacoVax*);
- messages with adverse events reported in *VigiFarmacoVax* (validated).

When the doctor validates the report in the *VigiFarmacoVax* platform, the same is automatically transferred to *VigiFarmacoVax*, where the project manager enters any missing information such as: ethnic origin of the child, coding of adverse events (using MedDRA terminology), AEFI outcome (complete resolution, hospitalization, not yet cured, etc.), date of onset of reaction (corresponding to the date of the vaccine administration), actions taken (administration of therapy, consultation with the pediatrician, etc.), batch and expiration of the vaccine, date, time, site of administration and pharmaceutical form (suspension for injection, powder for suspension for injection, powder for solution for injection, oral suspension). Finally, all the information entered is transferred, in a computerized manner, to the National Pharmaco-vigilance Network (RNF).

The received reports have been analyzed by number, gender, age distribution, type of suspected vaccine, adverse event, severity and outcome.

Data were anonymized and subsequently analyzed using Microsoft Excel 2007 software.

Given the limited number of MMR vaccine administrations, the latter was considered in the count of MMRV vaccines.

Adverse events characterized by the involvement of the same apparatus, or by a similar clinical presentation, were classified as belonging to the same group (for example, fever and low-grade fever were coded as "pyrexia").

Results

During the considered period, 1,494 consents were obtained for participation in the active vaccine vigilance project from the parents of 1,130 children, aged between 0 and 2 years.
Almost 66% (983; 65.8%) of those who gave their consent replied to the SMS.
A total of 1,984 doses of vaccine were given to these children; the highest number of administrations was recorded for the hexavalent vaccine (561; 28.3%), the 13-valent conjugated pneumococcal (555; 28%), the anti-rotavirus (338; 17%), and the meningococcal B (283; 14.3%) vaccines.
Of the 983 responses received from parents, 561 were validated as AEFI and reported a total of 1,248 adverse events.
Considering the defined criteria to establish the severity of a suspected adverse vaccine event, it emerges that almost all AEFI (558; 99.5%) were classified as "not serious"; 0.5% were classified as "severe" including upper respiratory tract infection, acute otitis and seizure.
Adverse events were grouped accordingly to Organ-Systemic Classification - SOC (MedDRA7 terminology), and this subdivision highlighted that most of the received reports were related to "General disorders and conditions related to the administration site" (653; 52.3%), followed by "Psychiatric disorders" (331; 26.5%) and by "Metabolism and nutrition disorders" (156; 12.5%).
Considering in detail the specific types of AEFI, pyrexia was the most frequent adverse event (468; 37.5%), followed by mood disorders (331; 26.5%), gastrointestinal disorders (156; 12.5%), local disturbances (116; 9.3%) and sleep disturbances (104; 8.3%) (Tab. III).

Conclusions

The study of the AEFI during the reporting period has allowed us to demonstrate how the start of an active surveillance project has led to a significant increase in reports.
However, it must be considered that the increase in reports and in awareness on the issue of vaccine safety may also be related to the increase in vaccination coverage and to the intense debate following the introduction of the mandatory vaccination law [8].
The innovative aspect of this project consists in the reduction of reporting times. Thanks to the use of mobile messaging (SMS), the time between the event following vaccination and reporting is reduced, especially in the case of minor events. The reduction of the time required for reporting can thus contribute to the qualitative and quantitative improvement of the transmitted information [9, 10].
Raising the awareness of health professionals and parents is of fundamental importance for the implementation of an effective vaccine vigilance system, especially at this time when the debate on vaccines is very active. In this context, the use of a direct and informal means of communication, such as messaging, for the reporting of adverse events, has proven to be a valid tool for involving users, as it makes parents perceive the health institution as a reference that is interested in the health of children even after the vaccination session.
The limits of the study concern the impossibility of knowing the outcome of the adverse event at the time of reporting, especially as regards the adverse events reported as "serious" and the lack of guarantee of equity in adhering to the study, given the need to know the Italian language and the need to be able to use mobile telephony as a reporting tool. However, the number of participants in the project and of the responses sent indicate the wide participation of parents. These data allow to speculate the possibility to extend this project to other realities of the national territory.
Continuous monitoring of vaccine safety and implementation of surveillance plans play a key role in achieving greater confidence in immunization programs and optimal vaccination coverage rate. Therefore, it is hoped that pharmacovigilance activity will increasingly become an essential part of the normal clinical practice; however, continuous training of health professionals is required to ensure greater willingness in communicating with citizens and make them more and more involved in monitoring activities.

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Conflicts of interest statement

The other authors declare no conflict of interest related to this manuscript. GG declares that he does not have a specific conflict of interest related to this paper; however, he reports grants from Sanofi Pasteur MSD, GSK Biologicals SA, Pfizer, Sanofi Pasteur Italy, MSD Italy, Emergent BioSolutions and Seqirus for taking part to advisory boards, expert meetings, for acting as speaker and/or organizer of meetings/congresses and as principal investigator and chief of O.U. in RCTs.

Authors' contributions

All the named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

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