Annual report on adverse events related with vaccines use in Calabria (Italy): 2012

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ABSTRACT

Vaccines are administered to large population of healthy individuals, particularly to millions of infants every year, through national immunization programs. Although vaccines represent a good defense against some infectious diseases, their administration may be related with the development of adverse vaccine events (AVEs); therefore their use is continually monitored to detect these side effects. In the presents work, we reported the suspected AVEs recorded in 2012 in Calabria, Italy. We performed a retrospective study on report forms of patients that developed AVEs in Calabria from January 1, 2012 to December 31, 2012. Naranjo score was used to evaluate the association between AVEs and vaccines and only suspected AVEs definable as certain, probable, or possible were included in this analysis. During the study period, we evaluated 461 records of adverse drug reactions (ADRs) and 18 (3.9%) were probably induced by vaccination. AVEs were common in females (almost 77.7%) and in children aged 0-3 years. The largest number of non-serious AVEs involved "skin and subcutaneous tissue disorders" and "general disorders and administration site conditions." In conclusion, we documented that in Calabria the total number of AVEs is very low and it may be useful to increase the pharmacovigilance culture in order to evaluate the safety of these products in large populations.

Key words: Adverse events, Calabria, children, immunization, vaccines

INTRODUCTION

Vaccines are administered to large population of healthy individuals, particularly to millions of infants every year, through national immunization programs.[1,2]

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The recommended childhood vaccination schedule has changed dramatically over the years, with children now receiving up to 20 vaccines, including multiple combination vaccines administrations, before the age of 6 years. The current Italian National Immunization Program is carried out through vaccination clinics within the Italian National Health Service. As some vaccinations are mandatory by law for all newborns (diphtheria, tetanus, poliomyelitis, hepatitis B) the network of vaccination clinics is capillary distributed all over the Italian territory.[3]

In Italy, the current vaccination schedule includes three doses of diphtheria, tetanus, acellular pertussis, poliomyelitis, hepatitis B, *Haemophilus influenzae* type

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b vaccine in the first year of life followed by a diphtheria, tetanus, acellular pertussis, and polio booster dose at 5-6 years of age. The first and second dose of measles, mumps, and rubella (MMR) vaccines are administered at 12-15 months and at 5-6 years, respectively. Additional booster doses of diphtheria, tetanus, and acellular pertussis vaccine (adult Tdap formulation) are recommended every 10 years [Table 1].

Although vaccines represent a good defense against some infectious diseases, their administration may be related with the development of adverse vaccine events (AVEs); therefore their use is continually monitored to detect both expected and unexpected side effects.[4,5]

Pharmacovigilance of vaccines is crucial since the size of clinical trials is insufficient to identify rare or deferred AVEs.[6]

AVEs can be specific, related to the antigen of an attenuated alive virus vaccine (lymphocyte meningitis after antimumps vaccine) or nonspecific, related to a component different from the antigen (aluminum hydroxide involved in the "macrophagic myofascitis," allergic reactions to neomycin, latex, egg, or gelatine).[6]

While vaccines may appear to be the causal factor leading to AVEs, other underlying patient medical conditions, including latent mitochondrial disease or vitamin deficiencies, may play a role.[7,8]

Differences in the individual immune system response to a vaccine may account for rare cases of individuals not protected following immunization or the appearance of side effects.[4,9,10]

Up to date, no data are available on vaccines' safety, therefore, the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) established a surveillance system to intensively monitor AVEs based on spontaneous reports.

Adverse events are defined as health effects that occur after immunization that may or may not be related to the vaccine.

In Italy, the signals of AVEs can be obtained with spontaneous reporting of medical records. Available data include the following information: Type of vaccine received, date of vaccination, manufacturer, lot number, and injection site, onset of AVE, current illnesses or medication, history of adverse events following vaccination, concurrent vaccinations (those given during the same visit) and demographic information about the recipient (age, gender, race). In the present work, we reported the suspected AVEs recorded in 2012 in Calabria, Italy.

MATERIALS AND METHODS

In agreement with our previous papers,[11-14] we performed a retrospective study on report forms of patients who developed AVEs in Calabria from January 1, 2012 to December 31, 2012.

Naranjo score was used to evaluate the association between AVEs and vaccines and only suspected AVEs definable as certain, probable, or possible were included in this analysis.[15]

We analyzed data with respect to source of reporting, gender, age, vaccine suspected of causing the event, seriousness, and system organ class (SOC).

Table 1: Vaccination schedule for infants and childhood in Italy

Age of child	Vaccines									
	DTaP	Hib	Hepa B	IPV	MMR	PVC	Men C	Varicella	Influenza	HPV
Birth			Yes							
3 months	Yes	Yes	Yes	Yes		Yes				
5 months	Yes	Yes	Yes	Yes		Yes				
6 months										
11 months	Yes	Yes	Yes	Yes		Yes				
	Yes	Yes	Yes	Yes		Yes				
13 months					Yes		Yes	Yes	Yes	
15 months	Yes		Yes	Yes	Yes			Yes		
24 months										
36 months										
5-6 years	Yes (dTaP)						Yes			Yes
11-12 years										
14-15 years										

DTaP=Difto-tetanus-acellular pertussis vaccine; dTaP=Difto-tetanus-acellular pertussis vaccine for adults; IPV=Inactivated antipolio vaccine; Hepa B=Hepatitis B vaccine (at birth only for newborns of HBsAg+mother; all others start immunization at 3 months of age); Hib=*Haemophilus Influenzae* type B vaccine; MMR=Measles, mumps, rubella vaccine; PVC=Pneumococcal heptavalent coniugate vaccine; MEN C=Meningococcal C coniugate vaccine; HPV=Human papilloma vaccine

RESULTS

During the study time-window, we found 461 records of adverse drug reactions (ADRs) and 18 (3.9%) were probably related to vaccination.

Our data shows that the sources of reporting were mainly doctors working in hospital (31.7%) [Figure 1], and AVEs were more common in females (almost 77.7%) and in the children aged 0-3 years [Table 2].

Five reports (27.7%) involved serious events that occurred with Priorix tetra®, a lyophilized mixed preparation of the attenuated Schwarz measles, RIT 4385 mumps (derived from Jeryl Lynn strain), Wistar RA 27/3 rubella and Oka varicella strains of viruses [Table 3].

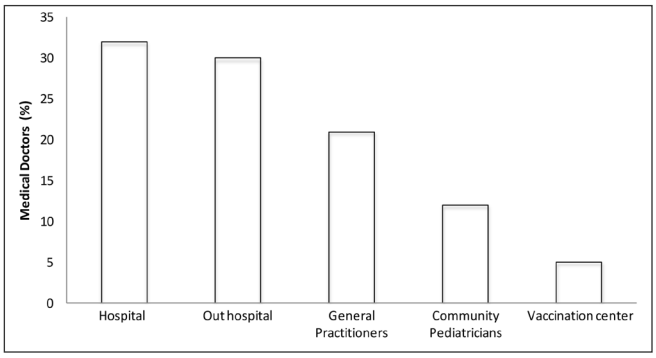

Figure 1: Medical doctors source of reporting

The largest numbers of non-serious AVEs involved "skin and subcutaneous tissue disorders" and "general disorders and administration site conditions" [Table 4].

DISCUSSION

In the present paper, we documented that 18 of 461 records of ADRs were probably related to vaccine administration in Calabria, Italy.

These data are lower in respect to the mean Italian data and probably it is related with the underreporting of ADRs in Calabria.

However, a previous Italian study documented an increased risk of developing immune thrombocytopenic purpura during MMR vaccine (odds ratio 2.4).[16] In our study, we did not record this skin manifestation, but we reported the development of serious AVEs (i.e., seizures) in 27.7% of records during the immunization with measles — mumps — rubella — varicella vaccine (MMRV) and with diphtheria and tetanus toxoids (DTP).

These data are in agreement with other papers that documented the development of seizures, after the immunization with DTP[17-20] and MMRV.[21]

In our study, we documented the development of apnea, cyanosis and muscular flaccidity in a 2-year-old girl after

Table 2: Total number of adverse drug reactions reported for vaccines by age group

	Age group (years)							
	<2	2-3	4-6	7-11	12-17	18-64	>65	Total ADRs
Vaccines								
Infanrix® (Diphtheria, tetanus, pertussis acellular, and poliomyelitis inactived)	3							3
Prevenar® (pneumococcalpolysaccharide)	1	1	1					3
Prevenar 13® (pneumococcalpolysaccharide serotype 13)						1		1
Priorix Tetra® (measles, mumps, rubella, varicella)		2						2
Meningitec® (meningococcal C coniugate)		1		1				2
Rudivax® (Attenuated rubella vaccine)						1		1
Cervarix® (nolive virus against HPV)					1			1
Intanza® ((Influenza virus inactivated, split)						2		2
Fluad® (Influenza Vaccine, Surface Antigen, Inactivated, Adjuvanted with MF59C.1)							2	2
Revaxis® (Diphtheria, tetanus and poliomyelitis inactived)						1		1

HPV=Human papilloma virus

Table 3: Reporting for suspected serious adverse events reported by age group

Age group (years)	<2	2-3	4-6	7-11	12-17	18-64	>65
ADRs serious							
Febrile convulsion	Prevenar®	Priorix Tetra®					
Seizure partial	Infanrix®						
Fever High, cyanosis, tremor		Priorix Tetra®					
Polyneuritis/arthralgy						Revaxis®	

Table 4: Reporting for suspected non-serious adverse events reported by age group

Age group (years)	<2	2-3	4-6	7-11	12-17	18-64	>65
ADRs non-serious							
Urticaria/Urticaria-like rash					Cervarix®	Prevenar 13®	
Injection Site (redness, swelling, pain)						Intanza®	
Apnea, cyanosis, muscular flaccidity		Meningitec®					
Lipotimia and vomiting			Prevenar®				
Erythema		Prevenar® Infanrix®		Meningetec®			
Fever		Infanrix®					
Rubella rash						Rudivax®	
Hyperglycemia							Fluad®

MENINGITEC® administration (see Table 2). Paradoxally, this event was reported as nonserious, although the child was admitted to intensive care unit.

In a previous study, Zhou *et al*.[22] evaluated, over 10 years, 128,717 reports with >1.9 billion doses of human vaccines administered in patients of all the age (from <1 year up to 64 years), and documented an higher number of AVEs in the age groups of 1-6 years (26.7%) and 18-64 years (32.65%). In this study, the most commons AVEs were fever, injection-site hypersensitivity and edema, and local vasodilatation.[22]

In agreement with this study, we documented that in adults the most common reactions were pain, redness, and swelling in the site of administration. These manifestations were nonserious with a favorable evolution.

Moreover, we reported the development of hyper-glycemia after administration of Fluad® in two elderly diabetic patients (aged 73 and 76 years, respectively).

However, up to date, no conclusive data are available concerning the association between vaccines and diabetes. In fact, although Classen *et al*.[23] documented an association between *Haemophilus influenzae* type b (Hib) vaccines and diabetes in children, two separate expert panels reviewing published data did not report a causal relationship between vaccines and diabetes.[24,25]

Unfortunately, we are not able to explain the possible association between vaccine and diabetes because several data were missing in the report form and this represents a limitation of this study.

In fact, spontaneous report of AVEs is a passive surveillance system, and the large number of reports increases the likelihood that some reports may not be adequately checked for accuracy.

In agreement with this point we documented that the higher number of AVEs were reported by hospital doctors, probably because hospital doctors are more prone to report AVEs, although it is also probable that they have more time to spend for the study of AVEs than for other studies.

Spontaneous reporting systems suffer from different barriers such as incomplete recognition of suspected ADRs; barriers to reporting and insufficient data quality, which may result in underreporting of important serious and rare ADRs. ADRs that are nonserious or known to be related to the vaccines may be over reported.[2]

The report forms often have a missing or incorrect data including comorbidity, vaccines coadministered, accurate descriptions of the event that occurred, and outcome of ADRs.

Some reports are likely to be unrelated to vaccinations. Nevertheless, spontaneous reports are still the source of information about new and previously unrecognized ADRs and an important postmarketing safety surveillance.[26]

The study of AVEs is a continuous process, starting from the initial reports and represents the door to studies of drug-epidemiology and quantitative risk assessment.[27,28] This is relevant for vaccines because it is not possible to know adverse effects during immunization due to limitations of clinical trials.[29,30]

Since vaccines are given to millions of infants annually, it is imperative that health authorities have scientific data from synergistic toxicity studies on all combinations of vaccines that infants might receive. Finding instruments to increase vaccine safety should be the highest priority.[1]

As vaccines are used in healthy people, their safety must be excellent to be accepted. Their monitoring after marketing is the sole way to detect rare ADRs. This surveillance is made through reporting of AVEs to the PVRC.[6]

In conclusion, we documented that in Calabria, the total number of AVEs is very low and it may be useful to increase the pharmacovigilance culture in order to evaluate the safety of these products in large population.

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