ARTICOLO ORIGINALE

UNDER-REPORTING OF ADVERSE EVENTS FOLLOWING IMMUNIZATION OBSERVED IN A SINGLE HOSPITAL SETTING IN ITALY

Mancata segnalazione di eventi avversi successivi all'immunizzazione osservata in un singolo setting ospedaliero in Italia

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Abstract
Introduction Spontaneous reporting system is widely used by pharmacovigilance centres. Its voluntary nature is the main cause of under-reporting of adverse drug reactions and adverse events following immunization (AEFIs). In literature, few studies explored the under-reporting phenomenon of AEFIs. The aim of this study was to investigate the under-reporting of AEFIs from healthcare professionals, by means of 44-month-long active pharmacovigilance study in a single hospital setting.
Methods In Senigallia Hospital (Italy), patients presented at the Emergency Department (ED) within the time window of 30 days after vaccine administration were identified retrospectively between January 1, 2014, and August 31, 2017. During the same period of time, the number of AEFIs officially reported by healthcare professionals working in the same hospital, to Pharmacovigilance National System, was evaluated.
Results In the 44-months study period, a total of 109,217 ED admissions occurred, of which 70 within 30 days after vaccine administration, with an overall prevalence of 0.6 per 1,000 ED admissions. We observed 162 AEFIs, of whom 58 were serious (36%) in 17 patients. 53 patients (76%) experienced 104 non-serious AEFIs, mainly related to fever, injection-site local reactions and gastrointestinal disorders. Overall, patients were mostly represented by Infants (43%) and Adult ≥65 years (23%). In the majority of cases, patients received only one vaccine (76%). The sex ratio of male to female was 0.9. ED presentation occurred at a mean of 5 days after vaccine administration. Of these 70 patients, only 4 ones who experienced non-serious events were officially reported to Pharmacovigilance National System by healthcare professionals. Causality assessment was performed in 61 cases. Considering the single-case judgment, in 44 patients (63%) the event was classified as "consistent" (35 and 9 cases in the "Non serious" and "Serious" events group respectively) and in 17 (24%) "inconsistent" (9 and 8 cases in the "Non serious" and "Serious" events group respectively).
Conclusions The number of AEFIs observed in this study is considerably larger than the number of events officially reported. Causality assessment allowed to demonstrate that the under-reporting from healthcare professional is not limited to events clearly not related to vaccination or to non-serious AEFIs. The single-centre nature of the study and the small sample size do not allow for the generalizability of results. However, given increasing public concern about risks associated with immunization, many strategies should be encouraged to improve this situation. It is likely that the most useful approach should be to take advantage of electronic vaccination registries linked to electronic healthcare databases for rigorous pharmacoepidemiological studies, in which associations between drug use and outcomes, as they occur in clinical practice, are assessed without relying on spontaneous reporting.

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Introduction

Post-marketing drug safety surveillance is a challenging and vital component of contemporary medical practice. Pharmacovigilance refers to the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects (AE) or any other drug-related problem [1]. Responsibility should be shared by the pharmaceutical industry, drug regulators, health professionals, patients, and the public.

Worldwide, the main source of information on the occurrence of adverse drug reactions (ADRs) and of adverse events following immunization (AEFIs) is the spontaneous reporting system (SRS). In this passive surveillance system, case reports of suspected ADRs/AEFIs are submitted to a national pharmacovigilance centre by healthcare providers, such as physicians, pharmacists, dentists and nurses, either directly or via the manufacturer of the drug. In some countries, including Italy, the national SRS provides an opportunity for direct reporting by patients.

The SRS has many advantages but also several limitations [2]. This system frequently depends on patient reporting of events that they experience during the use of a drug to healthcare professionals, who must recognize that the event could be an ADR/AEFI, complete a reporting form and submit it. This chain of events may never be started or, if it is, it is easily broken [3]. Therefore, under-reporting is a major problem with this system. According to a review on ADRs, published in 2006 [4], the median rate of under-reporting across 37 studies was 94% and there was no significant difference in the median under-reporting rates calculated for general practice and hospital-based studies. Under-reporting phenomenon among healthcare professionals also concerns drugs subject to additional monitoring and serious reactions including death [5]. Besides under-reporting problems, clinical information from spontaneously reported adverse events sometimes lacks essential data, such as temporal relationship, responses to challenges and/or re-challenge, and underlying patient condition, each one essential for identification of the causality of suspected drugs. Furthermore, analysis of passive surveillance data does not yield an incidence rate [4].

Given the deficiencies inherent in systems that rely on spontaneous reporting, there are other approaches to investigate causal relationship between medical interventions and harmful effects. In particular, active surveillance programs may supplement some weak points of SRS [6], using phone-structured interviews [7], ward rounds and chart review [8], computer monitoring [9], systematic clinical data mining [10].

Immunization is among the most successful and cost-effective public health interventions. Immunization safety has become as important as the efficacy of the national vaccine-preventable disease control programs. Unlike drugs, the expectations from vaccinations are much higher, and problems arising from the vaccine or vaccination are less acceptable to the general public [11]. Vaccines are usually administered to healthy people, including entire birth cohorts of infants, and in vast numbers. In many countries, specific vaccinations are mandatory for school admission as well as international travel. For these reasons, vaccines are drugs under additional monitoring, identified with a black inverted triangle displayed in their package leaflet and in the information for healthcare professionals. The concept of additional monitoring and the black symbol were introduced by European laws on the safety-monitoring of medicines, called the pharmacovigilance legislation, which started to come into effect in 2012 [12, 13].

The World Health Organization (WHO) defines AEFI any untoward medical occurrence that followed immunization with a consistent temporal relationship but that did not necessarily have a causal relationship with the usage of the vaccine [11]. In literature, few studies explored the under-reporting phenomenon of AEFIs. An active surveillance study in an out-patient setting in the Czech Republic identified a rate of AEFIs six times higher than the officially reported rate, although the vast majority of AEFI were non-serious and only 16% required medical attention [14]. The aim of the present study was to investigate the under-reporting of AEFIs from healthcare professionals by means of 44-month-long active pharmacovigilance study in a single hospital setting in Italy.

Methods

We conducted an active surveillance study on Emergency Department (ED) records of Principe di Piemonte Hospital of Senigallia, covering the period between January 1, 2014, and August 31, 2017. Patients presented at the ED within the time window of 30 days after vaccine administration were identified retrospectively, performing a search using keywords (vaccine, vaccination, tetanus, diphtheria, pertussis, polio, chickenpox, hepatitis, measles, mumps, rubella, trivalent, tetravalent, pentavalent, hexavalent vaccine, influenza, meningococcal, pneumococcal, haemophilus, rotavirus, yellow fever, rabies vaccine, papillomavirus, herpes zoster, tick-borne encephalitis, Japanese encephalitis, typhoid, cholera) from the database of ED clinical charts.

An AEFI was considered "serious" when it resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or resulted in other clinically relevant situations [15]. The description of the AEFI, according to diagnosis and symptoms, was coded using the Medical Dictionary for Regulatory Activities (MedDRA) and organized by System Organ Class (SOC) [16]. For the causality assessment of vaccine-related adverse drug reactions the specific WHO algorithm was used [11].

During the same period of time, the number of AEFIs officially reported by healthcare professionals working in the same hospital, to the National Pharmacovigilance Network (a database of Italian Drug Agency officially responsible for recording such events), was evaluated.

Descriptive statistics was used to summarize data. Categorical data were reported as frequencies and percentages, whereas continuous data were reported as means with standard errors. Data extraction was conducted independently by 2 members of the research team. Medical records consultation was performed having obtained the authorization from the Medical Records Department. The study was conducted following the principles of the Declaration of Helsinki [17].

Results

In the 44-months study period, a total of 109,217 ED admissions occurred, of which 70 within 30 days after vaccine administration, with an overall prevalence of 0.6 per 1,000 ED admissions. **Table 1** shows characteristics of patients.

Table 1 Characteristics of patients admitted to Emergency Department at Senigallia Hospital, from 01 January 2014 until 31 August 2017, for AEFIs.

		Non serious events	Serious events	Total
Involved patients N (%)		**53 (76)**	**17 (24)**	**70 (100)**
Sex (F/M)		27 F / 26 M	10 F / 7 M	37 F / 33 M
Tot AEFIs N (%)		104 (64)	58 (36)	162 (100)
N AEFIs/patient	1	27 (51.0)	2 (11.8)	29 (41.4)
	2	13 (24.5)	4 (23.6)	17 (24.3)
	≥3	13 (24.5)	11 (64.6)	24 (34.3)
N vaccines/patient	1	37 (69.8)	16 (94.1)	53 (76)
	2	7 (13.2)	1 (5.9)	8 (11)
	Not available	9 (17.0)	0 (0)	9 (13)
Age classes, years	Infants (<2)	28 (11 F / 17 M)	2 (1 F / 1 M)	30 (43)
	Children and Adolescent (≥2 – 17)	11 (6 F / 5 M)	3 (2 F / 1 M)	14 (20)
	Adult (≥18 - 64)	7 (5 F / 2 M)	3 (1 F / 2 M)	10 (14)
	Adult ≥65	7 (5 F / 2 M)	9 (6 F / 3 M)	16 (23)
Causality assessment (single-case judgment)	Consistent	35 (66.0)	9 (52.9)	44 (63)
	Inconsistent	9 (17.0)	8 (47.1)	17 (24)
	Ineligible	9 (17.0)	0 (0)	9 (13)
ED admission, days after vaccination (mean ± SD)		6 ± 4	5 ± 4	5 ± 4

We observed 162 AEFIs, of whom 58 were serious (36%) in 17 patients (11 patients were hospitalized, 1 refused the hospitalization, 5 experienced a clinically relevant condition - **Table 2**); 53 patients (76%) experienced 104 non-serious AEFIs, mainly related to fever, injection-site local reactions and gastrointestinal disorders (**Tables 3** and **4**).

Table 2 Serious adverse events following immunization (AEFIs) identified from the emergency department (ED) clinical charts database, at Senigallia Hospital, from 01 January 2014 until 31 August 2017.

Case	Calendar year	Sex	Age, years(y), months(m), days(d)	Vaccine type	ED admission, days after vaccination	Type of AEFI	Hospitalization	Causality assessment for each AEFI and final causality category
1	2014	F	92y, 7m	Influenza	7	tremor dizziness postural	-	1) Incons; 2) Incons → **Incons**
2	2014	F	92y, 7m	Influenza	3	hyperpyrexia vomiting dehydration	Yes	1) Cons; 2) Cons; 3) Incons → **Cons**
3	2014	F	86y, 5m	Influenza	about 15 hours after vaccination	abdominal pain vomiting acute cholecystitis	Yes	1) Incons; 2) Cons; 3) Incons → **Incons**
4	2015	F	88y, 1m	Influenza	10	dyspnea pulmonary embolism	Yes	1) Incons; 2) Incons → **Incons**
5	2015	M	47y, 1m	Influenza	6	hyperpyrexia pneumonia	-	1) Conc; 2) Incons → **Incons**
6	2015	M	77y, 5m	Influenza	7	hyperpyrexia confusional state coordination abnormal presyncope	-	1) Cons; 2) Incons; 3) Incons; 4) Incons → **Incons**
7	2015	F	87y, 11m	Influenza	5	hyperpyrexia vomiting diarrhoea abdominal pain septic shock	Yes	1) Cons; 2) Cons; 3) Cons; 4) Incons; 5) Incons → **Incons**
8	2016	M	1y, 3m, 22d	Meningo (a) + chickenpox (b)	3	hyperpyrexia vomiting diarrhoea dehydration	Yes	1a) Cons; 2a) Cons; 3a) Cons; 4a) Incons + 1b) Cons; 2b) Cons; 3b) Cons; 4b) Incons → **Cons**
9	2016	M	78y, 7m **(same patient of case 6)**	Influenza	about 10 hours after vaccination	hyperpyrexia tremor vomiting confusional state coordination abnormal presyncope jaundice	Yes	1) Cons; 2) Incons; 3) Cons; 4) Incons; 5) Incon; 6) Incon; 7) Incon → **Cons**
10	2016	M	71y, 2m	Tetanus	1	facial paralysis or Bell's palsy	-	Cons → **Cons**
11	2016	F	95y, 9m	Influenza	3	hyperpyrexia, haematochezia	Yes	1) Cons; 2) Incons → **Incons**

Case	Calendar year	Sex	Age, years(y), months(m), days(d)	Vaccine type	ED admission, days after vaccination	Type of AEFI	Hospitalization	Causality assessment for each AEFI and final causality category
12	2016	M	2y, 0m, 2d	Meningo	2	hyperpyrexia diarrhoea dehydration Salmonella enteritis	Yes	1) Cons; 2) Cons; 3) Incons; 4) Incons → **Incons**
13	2016	F	1y, 11m, 27d	Meningo	7	hyperpyrexia coordination abnormal constipation	Yes	1) Cons; 2) Cons; 3) Incons → **Cons**
14	2016	F	47y, 7m	Influenza	1	paraesthesia skin rash orbital oedema throat tightness (bi-phasic allergic reaction)	-	1) Cons; 2) Cons; 3) Cons; 4) Cons → **Cons**
15	2017	F	12y, 5m	Meningo	1	hyperpyrexia headache abdominal pain vomiting	Yes	1) Cons; 2) Cons; 3) Incons; 4) Cons → **Cons**
16	2017	M	36y, 6m	Meningo	10	hyperthermia photophobia headache	Refused by the patient	1) Cons; 2) Cons; 3) Cons → **Cons**
17	2017	F	3y, 2m, 19d	Meningo	15	febrile convulsion	Yes	Cons → **Cons**

***Cons**: consistent with causal association to immunization; **Incons**: inconsistent with causal association to immunization.*

Table 3 Non-Serious adverse events following immunization (AEFIs) identified from the emergency department (ED) clinical charts database, at Senigallia Hospital, from 01 January 2014 until 31 August 2017.

Case	Calendar year	Sex	Age - years(y), months(m), days(d)	Vaccine type	ED admission - days after vaccination	Type of AEFI	Causality assessment for each AEFI and final causality category
1	2014	F	59y, 9m	tetanus	7	hyperpyrexia vaccination site reaction (swelling, pain)	1) Cons; 2) Cons; 3) Cons → **Cons**
2	2014	F	93y, 7m	influenza	2	tremor	Incos → **Incons**
3	2014	F	84y, 0m	influenza	4	abdominal pain	Incons → **Incons**
4	2014	F	76y, 11m	influenza	1	dizziness confusional state abdominal pain	1) Incons; 2) Incons; 3) Incons → **Incons**
5	2014	F	0y, 9m, 5d	not available	5	hyperpyrexia diarrhea vaccination site reaction (swelling)	*Not applicable*
6	2014	F	1y, 4m, 16d	MMR (a)+ meningo (b)	7	hyperpyrexia	1a) Cons 1b) Cons → **Cons**
7	2014	F	1y, 8m, 6d	meningo	6	hyperpyrexia	Cons → **Cons**
8	2014	M	43y, 9m	tetanus	7	skin rash	Cons → **Cons**
9	2014	M	0y, 10m, 2d	typhus	15	skin rash	Cons → **Cons**
10	2014	F	5y, 2m	tetravalent (DPT-polio)	1	vaccination site reaction (erythema)	Cons → **Cons**

Case	Calendar year	Sex	Age - years(y), months(m), days(d)	Vaccine type	ED admission - days after vaccination	Type of AEFI	Causality assessment for each AEFI and final causality category
11	2014	F	54y, 7m	rabies	1	dizziness dyspnoea	1) Incons; 2) Incons → **Incons**
12	2015	M	1y, 8m, 30d	chickenpox	7	hyperpyrexia lymphadenopathy (submandibular)	1) Cons; 2) Cons → **Cons**
13	2015	M	5y, 4m	not available	5	hyperpyrexia dyspnea vomiting	*Not applicable*
14	2015	M	75y, 9m	influenza	2	dyspnoea cardiac failure acute	1) Incons; 2) Incons → **Incons**
15	2015	M	83y, 9m	influenza	6	dyspnoea cardiac failure acute	1) Incons; 2) Incons → **Incons**
16	2015	F	88y, 1m	influenza	3	hyperpyrexia, cough	1) Cons; 2) Cons → **Cons**
17	2015	M	0y, 11m, 19d	hexavalent	6	hyperpyrexia	Cons → **Cons**
18	2015	M	0y, 5m, 10d	not available	1	hyperpyrexia	*Not applicable*
19	2015	F	9y, 3m	yellow fever	15	hyperpyrexia abdominal pain vomiting	1) Cons; 2) Cons; 3) Cons → **Cons**
20	2015	F	0y, 3m, 25d	hexavalent (a) + pneumo (b)	1	hyperpyrexia	1a) Cons 1b) Cons → **Cons**
21	2016	M	0y, 5m, 11d	hexavalent (a) + pneumo (b)	5	hyperpyrexia tonsillitis skin rash (after intake of antibiotic)	1a) Cons; 2a) Incons; 3a) Incons 1b) Cons; 2b) Incons; 3b) Incons → **Incons**
22	2016	F	28y, 5m	yellow fever	5	hyperpyrexia diarrhoea,	1) Cons; 2) Cons → **Cons**
23	2016	M	1y, 4m, 27d	not available	12	hyperpyrexia cough vomiting diarrhoea	*Not applicable*
24	2016	M	10y, 1m	meningo	1	vaccination site reaction (swelling, pain)	1) Cons; 2) Cons → **Cons**
25	2016	M	1y, 0m, 26d	tetravalent (MMR, chickenpox)	9	hyperpyrexia	Cons → **Cons**
26	2016	M	1y, 1m, 17d	not available	7	hyperpyrexia	*Not applicable*
27	2016	F	1y, 3m, 1d	MMR	8	hyperpyrexia	Cons → **Cons**
28	2016	F	2y, 10m, 16d	MMR	7	hyperpyrexia	Cons → **Cons**
29	2016	F	1y, 6m, 23d	MMR	10	hyperpyrexia skin rash	1) Cons; 2) Cons → **Cons**

Case	Calendar year	Sex	Age - years(y), months(m), days(d)	Vaccine type	ED admission - days after vaccination	Type of AEFI	Causality assessment for each AEFI and final causality category
30	2016	M	1y, 3m, 10d	hexavalent (a) + MMR (b)	15	hyperpyrexia	1a) Cons + 1b) Cons → **Cons**
31	2017	M	4y, 1m	chickenpox	4	vomiting	Cons → **Cons**
32	2017	M	5y, 4m	meningo	6	hyperpyrexia vaccination site reaction (joint pain, joint movement impairment)	1) Cons; 2) Cons; 3) Cons → **Cons**
33	2017	M	0y, 5m, 6d	not available	4	hyperpyrexia, cough, decrease appetite	*Not applicable*
34	2017	M	11y, 8m	meningo	15	fatigue dizziness	1) Incons; 2) Cons → **Incons**
35	2017	F	1y, 6m, 25d	MMR	10	hyperpyrexia cough	1) Cons; 2) Incons → **Cons**
36	2017	M	0y, 8m, 16d	not available	4	hyperpyrexia dyspnea vomiting persistent crying	*Not applicable*
37	2017	F	50y, 6m	influenza	0	paraesthesia oral vaccination site reaction (paraesthesia, joint pain, joint movement impairment)	1) Incons; 2) Cons; 3) Cons; 4) Cons → **Cons**
38	2017	F	9y, 5m	meningo	8	vaccination site reaction (joint pain)	Cons → **Cons**
39	2017	F	8y, 3m	meningo	2	headache	Cons → **Cons**
40	2017	M	0y, 6m, 25d	tetanus	5	hyperpyrexia persistent crying dyspnoea	1) Cons; 2) Cons; 3) Incons → **Cons**
41	2017	F	1y, 4m, 17d	meningo	2	hyperpyrexia cough	1) Cons; 2) Incons → **Cons**
42	2017	F	1y, 0, 26d	tetravalent (MMR, chickenpox) (a) + meningo (b)	10	hyperpyrexia	1a) Cons 1b) Cons → **Cons**
43	2017	M	0y, 2m, 20d	tetravalent (DPT-polio) (a) + pneumo (b)	5	hyperpyrexia	1a) Cons 1b) Cons → **Cons**
44	2017	F	0y, 4m, 12d	not available	1	hyperpyrexia	*Not applicable*
45	2017	M	1y, 2m, 22d	not available	10	hyperpyrexia cystitis	*Not applicable*
46	2017	M	1y, 1m, 24d	MMR	4	hyperpyrexia	Cons → **Cons**
47	2017	F	8y, 4m	meningo	0	dizziness	Cons → **Cons**
48	2017	F	1y, 2m, 30d	hexavalent	2	hyperpyrexia vomiting asthenia	1) Cons; 2) Cons; 3) Incons → **Cons**
49	2017	M	1y, 1m, 24d	chickenpox	20	skin rash	Cons → **Cons**

MMR: measles, mumps and rubella vaccine; DPT-polio: diphteria, tetanus, pertussis and poliomyelitis vaccine; ***Cons****: consistent with causal association to immunization;* ***Incons****: inconsistent with causal association to immunization.*

Table 4 Non-Serious adverse events following immunization (AEFIs) identified from the emergency department (ED) clinical charts database, at Senigallia Hospital, from 01 January 2014 until 31 August 2017 and officially reported to Pharmacovigilance National System.

Case	Calendar year	Sex	Age, years (y), months (m), days (d)	Vaccine type	ED admission-days after vaccination	Type of AEFI	Causality assessment for each AEFI and final causality category
1	2015	M	0y, 5m, 17d	hexavalent	0	hyperpyrexia vomiting	1) Cons; 2) Cons → **Cons**
2	2016	F	67y, 2m	tetanus	not available	dysphagia	Incons → **Incons**
3	2016	M	60y, 10m	yellow fever	not available	abdominal pain	Cons → **Cons**
4	2017	F	26y, 11m	DTP (a) + meningo (b)	0	Presyncope (vaso-vagal reaction)	1 a) Cons 1 b) Cons → **Cons**

DTP: diphteria, tetanus, pertussis vaccine; ***Cons****: consistent with causal association to immunization;* ***Incons****: inconsistent with causal association to immunisation.*

Overall, patients were mostly represented by infants (43%) and adult ≥ 65 years (23%). In the majority of cases, patients received only one vaccine (76%). In the "Non-serious events group" the majority of patients experienced only one AEFI; on the contrary, in the "Serious events group" the majority of patients experienced three or more AEFIs. The ratio of male to female was 0.9. ED presentation occurred at a mean of 5 ± 4 days after vaccine administration. Of these 70 patients, only 4 ones who experienced non-serious events were officially reported to Pharmacovigilance National System by healthcare professionals (**Table 4**).

Causality assessment was performed in 61 cases; the remaining 9 cases (13%) were ineligible because vaccine type was not available (**Table 1**). Globally 93 AEFIs were classified as "consistent" with causal association to immunization and 47 "inconsistent". Considering the single-case judgment in 44 patients (63%) the event was classified as "consistent" (35 and 9 cases in the "Non serious" and "Serious" events group respectively) and in 17 patients (24%) "inconsistent" (9 and 8 cases in the "Non serious" and "Serious" events group respectively).

Table 5 shows the distribution of AEFIs according to SOC classification. The most frequently reported SOCs were: general disorders and administration site conditions (39%), followed by gastrointestinal disorders (19%) and nervous system disorders (15%).

Table 5 Distribution of AEFIs according to System Organ Class (SOC) classification.

	Tot AEFIs N (% out of 162)	Serious AEFIs N (% out of corresponding SOC)
SOC		
General disorders and administration site conditions	64 (39.5)	12 (19)
Gastrointestinal disorders	31 (19.1)	16 (52)
Nervous system disorders	25 (15.4)	14 (56)
Cardiac disorders	9 (5.6)	1 (11)
Respiratory, thoracic and mediastinal disorders	9 (5.7)	2 (22)
Skin and subcutaneous tissue disorders	7 (4.3)	1 (14)
Metabolism and nutrition disorders	5 (3.2)	3 (60)
Psychiatric disorders	4 (2.5)	3 (75)
Infections and infestations	2 (1.2)	2 (100)
Blood and lymphatic system disorders	2 (1.2)	1 (50)
Eye disorders	2 (1.2)	2 (100)
Renal and urinary disorders	1 (0.6)	0 (0)
Hepatobiliary disorders	1 (0.6)	1 (100)

Discussion

In this study, we retrospectively collected data on AEFIs observed in the ED of a single hospital, over a 44-month period. The number of identified AEFIs is considerably larger than the number officially reported to Pharmacovigilance National System. As established by the WHO [11], even if some cases might seem not related to vaccination, they should be equally reported. It is important not to disregard any AEFI, because at some point similar events may be considered a "signal" and may lead to hypotheses regarding a link between a vaccine and the event in question, with specific studies designed to test for a causal association. For example, cases of cholecystitis, pneumonia, sepsis, enteritis etc., following vaccination should be reported to Pharmacovigilance National System, to survey that vaccinations don't contribute to the onset or progression of such inflammation/infection events [18]. Adverse events, especially those that result from drug–drug or drug–clinical context interactions, presumably are more likely to occur among the sicker and more complex patient population, making them harder to discover [10].

As described in literature, the most frequently observed AEFIs were fever/hyperpyrexia [19] and vaccination injection site reactions [20]. One case of severe bi-phasic allergic reaction was observed in a 47-year-old female after influenza vaccination [21].

Causality assessment allowed to demonstrate that the under-reporting from healthcare professional is not limited to events clearly not related to vaccination or to non-serious AEFIs.

Several limitations need to be considered when interpreting results of the present study. First, the single-centre nature of the study and the small sample size do not allow for the generalizability of results. Second, the retrospective nature of the study may have led to an underestimation of the number of ED admissions identified, as a result of missing or inaccurately documented clinical data. Frequently, patients do not communicate vaccine information to the nurse or physician because they do not consider their symptoms to be related to vaccination administered days or weeks before. On the other hand, when a patient relates his or her vaccination-related symptoms, nurse or physician frequently consider a causal relationship to be improbable and they do not report this information in the clinical chart.

Under-reporting of ADRs is a well-recognized problem, worldwide [3-5]. Nevertheless, few studies explored under-reporting of AEFIs. It is known that active surveillance provides better case identification than passive surveillance [6, 14, 22]. In fact, we confirmed this difference. Similar active surveillance studies could be useful to highlight the under-reporting phenomenon of AEFIs in others in-patient and out-patient settings in different countries. There is need to sensitize and train healthcare professionals in post-licensure surveillance of AEFIs. This is a fundamental activity to improve safety and maintain public confidence in these crucial medicinal products.

Which policies could be used? SRS provides the highest volume of information. Continuing training of healthcare professionals and education of the general public about pharmacovigilance and about all possible AEFIs are essential [23, 24]. This is a pivotal aspect for healthcare workers in vaccine centres, paediatricians, family doctors and emergency care practitioners. Compulsory and not voluntary reporting from doctors could be considered [25]. A Chinese experience demonstrated that a financial intervention based on a fine and a bonus significantly improved spontaneous reporting of ADRs by physicians in a hospital setting [26]. However, reporting would still depend on medical suspicion of a possible causal relationship with the product in question. Active surveillance studies, even if more efficient than SRS, as confirmed by our results, can be complex and costly to implement [6, 27]. The digitization of the healthcare industry is needed to try to overcome these last limitations. Electronic vaccination registries [28-29] are warranted together with other electronic healthcare databases (general practitioners, in- and outpatient pharmacies, clinical laboratories, hospitals, cancer registries, pathology registries, perinatal registries); they should be "linked" on a patient level through validated algorithms for as complete as possible capture of both vaccine exposure and medical visit outcomes [30, 31]. This kind of health digitalization should prevent the verification of the effectiveness and safety of vaccines from relying mainly on the "goodwill" of some healthcare professionals or patients.

Conclusions

The problem of under-reporting of ADRs to SRS (or public health passive surveillance system) has been well recognized for many decades. Few studies explored the under-reporting phenomenon of AEFIs. In this study we observed a relevant number of AEFIs that weren't reported to Pharmacovigilance National System by healthcare professionals. The single-centre nature of the study and the small sample size do not allow for the generalizability of results. However, given the increasing public concerns about risks associated with immunization, many strategies should be encouraged to improve this situation. There is no easy solution. It is likely that the most useful approach should be to take advantage of electronic vaccination registries linked to administrative healthcare databases for rigorous pharmacoepidemiological studies, in which associations between drug use and outcomes, as they occur in clinical practice, are assessed without relying on spontaneous reporting. This would allow the SRS to continue to be used for signalling unusual, new, or clusters of known AEFIs.

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