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SYSTEMATIC USE OF CAUSALITY ASSESSMENT IN AEFI SURVEILLANCE: A 2013-2016 PILOT STUDY IN PUGLIA

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ABSTRACT

Causality assessment is an algorithm proposed by WHO to identify a causal relationship between vaccines and adverse events following immunization (AEFIs), mostly for serious adverse events. It can be considered consistent, inconsistent, indeterminate or unclassifiable.
This study describes AEFIs reported in Puglia from 2013 to 2016 and analyzes the differences between the causality assessments performed on AEFI case-report information and the causality assessments performed after the examination of clinical documentation.
292 AEFI were reported: 191 (65.4%) non serious, 59 (20.2%) serious and 42 (14.4%) undefined. Causality assessment performed on the AEFI case-report information classified 59.2% (n=29/49) of serious AEFIs as consistent while assessment performed after clinical review only classified 30.6% (n=15/49) of serious AEFI as consistent (X2=65.0; p=0,000). In the first approach, inconsistent serious AEFIs were 18.6% (n=11/49) and then became 45.8% (n=27/49) after examination of clinical documentation. Indeterminate serious AEFIs were 6.8% (n=4) at first, and then 3.4% (n=2). Unclassifiables did not change.

1. Introduction

According to the current opinion of the scientific community, improved health correlated with recommended vaccinations, both for children and adults, is significantly higher than the risk of adverse events, because severe adverse events following immunization (AEFIs) are absolutely rare [1].

Vaccinations are usually administered to healthy persons and are mandatory in several countries. For this reason, they are held to a higher standard of safety than other medical products, both through pre-licensure safety evaluations and post-marketing surveillance activities [2].

AEFIs are unexpected medical occurrences following immunization, and they do not necessarily have a causal relationship with the vaccine. Adverse events may be unfavourable or unintended markings, an abnormal laboratory finding, a symptom or a disease [3].

AEFIs are classified as follows: *vaccine product-related reaction* - an AEFI caused or accellerated by a vaccine due to one or more of the inherent properties of the products; *vaccine quality defect-related reaction* - events related to the use of a vaccine or an administration device with some quality defects; *immunization error-related reaction* - AEFI caused by inappropriate vaccine handing, prescribing or administration; *immunization anxiety-related reaction* - related to the anxiety about the immunization; *coincidental event* - event only temporary related to the vaccine administration and caused by concomitant facts [4].

In post-marketing surveillance programs, all adverse events must be detected and reported to improve product safety and management. AEFIs can be categorised as serious, not serious or undefined events. Serious events result in death or life-threatening circumstances, require inpatient hospitalization or prolongation of existing hospitalization, cause persistent or significant disability/incapacity, congenital anomalies or birth defects. We can also include in this group the occurrence of events with greater frequency than expected or those of unusual severity [5-6].

Several criteria are relevant in defining the link between a vaccine and a specific adverse event: *temporal relationship* (vaccination must precede adverse event), *strength of association*, *biological plausibility* (the association should be compatible with existing theory and knowledge related to how the vaccine works), *evidence or absence of alternative etiological explanations*, and *de-challenge or re-challenge* [7].

Causality assessment is an algorithm proposed by WHO to identify a causal relationship between vaccines and adverse events. The systematic

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use of this algorithm is strongly reccomended for serious adverse events. Causality assessment usually will not prove or disprove an association between an event and the immunization. It is meant to assist in determining the level of certainty of an association. The assessment of a single event is not consistent with the purpose of identifying a definite causal association or the absence of association. In March 2013. WHO and CIOMS published the last update of systematic and standardized causality assessment processes for serious AEFI to be used by staff of national immunization programs, regulatory authorities, and pharmacovigilance or surveillance departments [6-8].

Despite WHO recommendations, there are few examples of post-marketing AEFI surveillance studies in scientific literature, and the AEFI causality assessment protocol does not seem to be used in scientific research or in the current practice of National Agencies [9-10-11].

The definition of causality assessment of each AEFI includes: an eligibility component for the assessment that reviews the diagnosis associated with the event and identifies the administered vaccines; a checklist that systematically guides users to gather available information to feed a decision algorithm; a decision support algorithm that assists the public health authorities in the classification of the AEFI [5-12].

The association between vaccine/AEFI can be considered *unclassifiable* when AEFI's data reported are inadequate or incomplete; *indeterminate* if there isn't clear evidence for a causal link, or conflicting trends, or inconsistency with causal association to immunization; *consistent* or *inconsistent* in presence or absence of a defined causal relationship with the immunization. The standardized definitions of AEFIs and causality assessment are necessary as guidelines for the collection, analysis and presentation of surveillance data [13-14-15].

The Italian Authority for Drugs (AIFA) recommends that causality assessment be performed only according to information obtained from AEFI case-reports. One must consider that inadequate or incomplete information could mislead the classification of the event. To define causality assessment, time of vaccine exposure, time of the occurrence of the adverse event, all details of the vaccine administered, unfavourable or unintended markings, abnormal laboratory findings, and symptoms or diseases in question should be available.

According to Italian Law, the notification of supposed AEFIs is mandatory for health care workers, and patients can report events potentially related to vaccinations to health authorities [16].

AEFIs and causality should be added to the National Network of Pharmacovigilance operating in connection with the European network for pharmacovigilance EudraVigilance that collects all data provided at national level by the EU countries in a single data warehouse [17-18].

This study seeks to describe AEFIs reported in Puglia from 2013 to 2016, and the distribution by seriousness, year, sex, age group and by vaccine administered. This study also analyzes the differences between causality assessment of serious events based exclusively upon information of AEFI case-reports against those of causality assessments performed after the examination of complete clinical documentation (for example, clinical record, in the case of hospitalization) [19-20].

2. Material and Methods

From January 1, 2013 to Decembre 31, 2016, 292 spontaneous AEFIs were reported in Puglia and collected through the National Network of Pharmacovigilance. An AEFIs list was added in Microsoft Office Excel database while data analysis was performed with STATA MP12.

The evaluation of causality assessment was performed using the algorithm proposed by WHO (last update version in March 2013), and approved in Italy by AIFA's working group.

For serious AEFIs, which result in hospitalization or in emergency department visits, clinical documentation (such as hospital discharges) was required.

The causality assessment was first performed using only information from AEFI case-reports (STEP 1) without consulting clinical documentation. The causality assessment was then repeated considering clinical documentation (STEP 2).

To compare the two assessments, categorical variables were expressed as proportions. Fisher's chi-square test and chi-square test were used for comparison. Significance was assumed for $p<0.05$.

3. Results

Out of 292 AEFIs reported in the database, 148 (50.7%) regarded men and 144 (49.3%) women. 191 (65.4%) AEFIs were reported as non-serious adverse events, 59 (20.2%) as serious and 42 (14.4%) as undefined. There were no significant differences in the distribution of adverse events per gender and severity ($X2 = 0.2$; $p = 0.906$) (Figure 1).

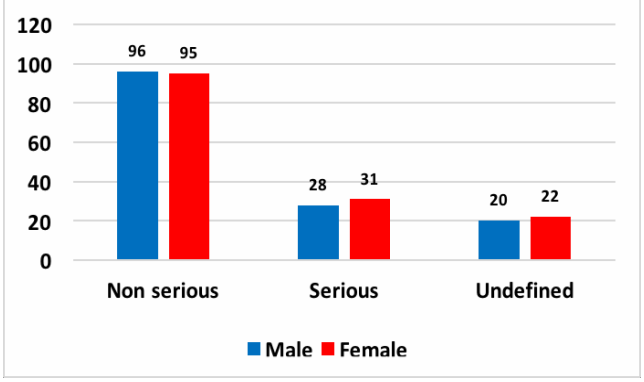

Figure 1 - AEFI's distribution per gender and severity

Table 1 describes the distribution of the sample per year of onset of AEFIs and age group of the vaccinated subjects: in 2013 (n=54; 58.1%) and 2016 (n=38; 45.7%) there was a higher percentage of AEFIs in vaccinated children of 1 - 6 years, while in 2014 a higher percentage of AEFIs was reported in subjects >6 years old (n=26; 56.5%) ($X2 = 122.0$, $p = 0.000$).

The distribution of AEFIs per year of onset and gender did not show significant difference (X2 = 3.2, p = 0.364). Table 2 shows the distribution of AEFIs per severity and composition of vaccine.

Age class	Year of ADRs onset							
	2013		2014		2015		2016	
	n	%	n	%	n	%	n	%
< 1 year	19	20.4	5	10.9	38	45.8	14	20.0
1-6 years	54	58.1	15	32.6	25	30.1	32	45.7
> 6 years	20	21.5	26	56.5	20	24.1	24	34.3
Totale	93	100.0	46	100.0	83	100.0	70	100.0

Table 1 - AEFIs distribution per year of onset and age class

Vaccine	ADR severity					
	Non serious		Undefined		Serious	
	n	%	n	%	n	%
Viral	97	50.8	21	50.0	38	64.4
Bacterial	59	30.9	14	33.3	10	17.0
Mixed	35	18.3	7	16.7	11	18.6
Total	191	100.0	42	100.0	59	100.0

Table 2 - Distribution of AEFIs per severity and composition of vaccine (Viral, Bacterial, Mixed)

Serious adverse events have most frequently been reported after administration of viral vaccines (Flu adjuvated vaccine = 17%; MMRV = 11.3%; 4HPV = 5.0%; MMR = 1.7%, other viral vaccines = 25.4%); non-serious reactions have been reported more frequently after administration of Men B (n = 41; 21.5%); non-defined ADRs have been reported after MMRV (n = 15; 35.7%). From 2013 to 2016, 59 serious AEFIs were reported; clinical documentation is available for 49/59 AEFIs.

For this group we implemented two different steps:

- STEP 1: Causality assessment performed only according to AEFI case-report information
- STEP 2: Causality assessment performed after viewing the clinical folder (concerning hospitalization or emergency department visits)

In step 1, the majority of AEFIs were classified as *consistent* (n = 29; 59.2%), while 11 were considered *inconsistent* (22.4%), 4 *Indeterminate* (8.2%) and 5 *unclassifiable* (10,2%).

In step 2, *consistent* serious AEFIs were 15 (30.6%), while 27 were defined as *inconsistent* (55.1%), 2 of 49 *indeterminate* (4.1%) and 5 of 49 *unclassifiable* (10,2%).

The distribution of AEFIs for results of assessment in step 1 and step 2 resulted statistically different (X2 = 65.0; p = 0.000) (Figure 2).

In the distribution of causality assessment by step of evaluation and type of vaccine, an important increase in adverse events considered inconsistent resulted. A higher increase was reported for viral vaccines.

The sample did not have the statistical power to investigate the difference between step 1 and step 2 per vaccine type (Table 3).

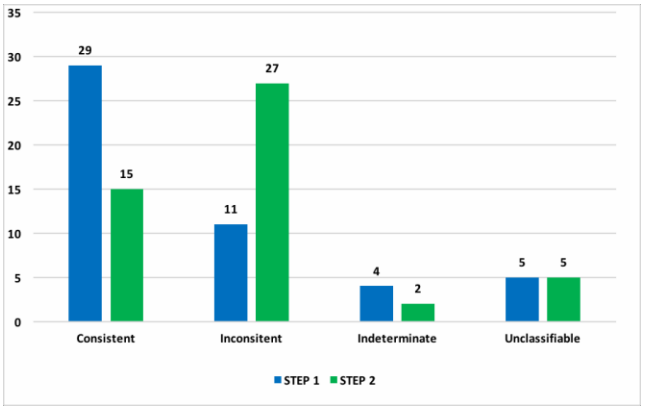

Figure 2 - Distribution of causality assessment by step of evaluation

Causality assessment evaluation	Type of vaccine					
	Viral		Bacterial		Mixed	
	n	%	n	%	n	%
Step 1						
Inconsistent	8	25.8	2	25.0	1	10.0
Consistent	17	54.8	4	50.0	8	80.0
Unclassifiable	2	6.5	2	25.0	1	10.0
Indeterminate	4	12.9	0	0.0	0	0.0
Total	31	100.0	8	100.0	10	100.0
Step 2						
Inconsistent	20	64.5	3	37.5	4	40.0
Consistent	9	29.0	2	25.0	4	40.0
Unclassificable	2	6.5	2	25.0	1	10.0
Indeterminate	0	0.0	1	12.5	1	10.0
Total	31	100.0	8	100.0	10	100.0

Table 3 - Distribution of causality assessment definition by step of evaluation and type of vaccine (viral, bacterial, mixed).

4. Discussion

Puglia is considered to be one of Italy's most active regions for the prevention of infectious diseases, with particular reference to the definition and update of vaccine prevention programs.

Annual AEFI's reporting rate in Puglia resulted significantly lower than the national one: in 2013 this figure was 4.8 x 100.000 doses, in 2014 4 x 100,000 and in 2015 5 x 100,000 doses, where as the Italian reporting rate in 2013 was 18 x 100000 doses and in 2015 19 x100,000 dose. Thanks to post-marketing active surveillance, in 2014 the Italian reporting rate was 49 x 100000 doses [21-22].

Indeed in Puglia, above all, there is a low tendency to report non-serious AEFIs that resulted in only 54.4% of total AEFIs in 2014 and 56% in 2016, while in overall Italian reporting of non-serious AEFIs represented over 80%. The data suggest that, despite the low rate of AEFI reporting, the passive surveillance system would be solid to detect safety signals which are expected following changes in the immunization program, allowing these to be investigated further [22].

The number of reported AEFIs changes over the years used in this study and in the different age groups. In particular, the proportion of serious ADRs was higher in 2014 (X2 = 122.0; p = 0.000).

This phenomen could be related to the so-called "Fluad case", namely the reporting of deaths only temporarily associated with the administration of adjuvanted anti-influenza vaccines, which involved the cautious retrieval of the vaccine. The retrieval induced a hesitant media mechanism in increasing the reporting of suspected ADR serious side effects after administration of the influenza vaccine [23].

In another Italian situation, as a consequence of lack of adverse effect public reporting, a supposed AEFI, only temporarily-related to a vaccine and without any causality assessment, was thoughtlessly published, forcing Public Health Authorities to respond promptly in order to avoid panic among the general population. [24]

From the analysis of the results obtained, the importance of obtaining comprehensive and detailed health documentation is evident to enable the pharmacovigilance manager to properly assess the causal link between the adverse reaction and the vaccination. The significant difference between step 1 and step 2 suggests the need for the regional pharmacovigilance manager to have all of the information. Probably, official recommendation about the causality assessment of AEFIs must be updated and the use of clinical documentation must be mandatory.

The serious AEFIs (death, disability, cluster and hospitalization) need to be reported immediately and investigated in detail as per the WHO established procedures. Physicians need to be trained to properly complete AEFIs reports with clinical report consultation being an indispensable element of AEFI evalutaion. Additionally, in the event of a serious reaction, people in charge of pharmacovigilance must verify the availability of medical records regarding access to Emergency room or hospitalization, with the ultimate aim of limiting, as far as possible, the margin of error in the evaluation of causality assessment of ADRs [25]. Furthermore, a precise and accurate communication report of AEFIs should be provided by Public Health Authorities to reinforce the trust in vaccination programs among the general population [26]

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