Factors associated with adverse events following immunization in Albanian children: An analysis of the national database of adverse events after immunization

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ABSTRACT

Background: Adverse events following immunization are a major concern which is influencing vaccination coverage all over the world. It is therefore important to evaluate the reporting of this events and factors associated with their occurrence in order to prevent them.
Methods: The national database of adverse events following immunization in Albanian children was de-identified and transferred to the IBM® SPSS version 21. (SPSS Inc, USA). Every medical information was re-entered using the Medical Dictionary for Regulatory Activities (MedDRA) terms. The dose-based reporting rates are calculated always taking in consideration the number of administered vaccines instead of the number of distributed ones, which is an advantage of the Albanian reporting system
Results: During a thirteen year period (2003-2015) there have been 307 AEFI cases reported for a total of 7,713,325 doses of vaccines administered. That regarded 106 females and 134 males. Most of the events have been reported during 2004. Most of thecases were non-serious (78,8%).
Most of the cases were treated at ambulatory setting (72.55), followed by hospital treatment (24.3%) and no treatment (2.6%). Most of the cases were recorded in infants aged < 4 months.
Conclusion: During the 13 year period, there were no severe events. The completeness and accuracy of information in the Albanian vaccine safety surveillance system still need to improve.

Key words: Adverse events following immunization, vaccines, reporting rates, immunization.

INTRODUCTION

Albania is a high-middle income country with a mean annual birth of 35 000 children and a mean value of total administered vaccines annually of 590,000 doses. The vaccination program in Albania was established in 1960. Before 1990 most of the vaccines of the national immunization schedule were produced in Albania (BCG, DTP and measles) except the oral polio virus (OPV) which was imported from abroad, covering, in this way, all the country's needs. In Albania, vaccination is mandatory by the law No.15/2016 "For the prevention and control of infectious diseases" which states that immunization is obligatory for children aged 0-18 years old. (Art.8) and it is one of the requisites for registration in school [1]. Children aged from 0-18 years old are immunized against 12 infectious diseases ; Tuberculosis (BCG vaccine administered soon after birth) , Hepatitis B (HepB), Diphteria, Tetanus, Pertussis (DTP-HepB-Hib vaccine administered at 2,4 and 6 months of age, DTP vaccine administered at 2 years old, DT vaccine administered at 6 years old, Td vaccine administered at 14 and 18 year old), Haemophilus influenzae type b (Hib vaccine), Measles, Mumps, Rubella (MMR vaccine administered at 1 and 5 years old), Pneumococcal (PCV vaccine administered at 2,4 and 10 months) and Polio(IPV and OPV vaccine given at 2,4,6 months and 2, 6 years old children). Immunization service providers in Albania include maternity hospitals and child consultancies situated at primary health care services in urban areas and rural areas.

The AEFI reporting system in Albania started in 2001 with the establishment of the National Regulatory Authority of Vaccines in the IPH. Before 2000, the reporting of any adverse event was ad hoc within the national immunization program [2]. The real steps toward establishment of vaccine safety surveillance system started in 2003 with the introduction of a standardized AEFI reporting form to all immunization provider units. Along with the AEFI reporting form, a list of reportable adverse events was distributed, a guideline of how to report and the treatment protocol for each possible occurring event after vaccination. Albania is divided administratively into 36 districts and each district has its own epidemiological laboratory.

Considering that the national Adverse Events Following Immunization (AEFI) surveillance system has already been running for 14 years, it is timely to investigate the reporting rates. The reporting of AEFI in Albania is conducted through (AEFI) reporting forms. During this period of time, the total vaccination coverage has ranged from 97,2%-99,2%. In this study, we attempted to identify the factors that influence the occurrence of AEFI and their patterns in order to detect any relevant relationship between them. Moreover, we aimed to calculate reporting rates in order to identify any underreporting and reasons related to it. Unlike most of the European countries, in Albania it is still used the cellular Pertussis vaccines which is responsible for most of the reported events. Traditionally produced whole cell Pertussis vaccine (wP) contains large quantities of endotoxin, which is a major factor contributing to local and systemic adverse events in humans [3]. About 35–60% of the endotoxin is released in the solvents during the first week of vaccine storage and up to 80% after 5–6 months [4]. Considering this information, we attempted to evaluate the relationship between storage time of wP containing vaccines in Albania and adverse events following this vaccine. Unfortunately, data about this variable were available only for 85 cases (27.6%).

METHODS

The AEFI data used in the study were received from the national database of adverse events following immunization situated in the Albanian Institute of Public Health.. Registered cases were children aged from 0-18 years old reported from 2003 to 2015. After the removal of names and surnames of each case, a progressive number was assigned to each case. The database was checked for duplicates, missing information and empty rows. No duplicated case was recorded. The information in the database was confronted with the information contained in the aggregated AEFI reporting forms received from vaccination points from 2003 to 2015. If the information was not obtained either from the individual AEFI reporting forms, vaccination point from where the form was received was asked through a telephone call. Every medical information was re-entered using the Medical Dictionary for regulatory activities (MedDRA) terms. The criteria used to classify a case as serious or non serious included; hospitalization of the patient which was extracted from the type of treatment received by the patient (ambulatory or hospital), clinical relevance of the event, outcome of the event at the time of reporting and the concomitant presence of other clinical events.

Statistical analysis

Statistical analysis is performed through IBM® SPSS version 21. (SPSS Inc, USA) and R statistical packages. Statistical significance was asset at $P \leq 0.05$. Qualitative data were expressed in terms of frequency and percentage, while quantitative data in terms of mean+-standard deviation. The reporting rates of cases are calculated as follows: RRC= No. of cases/ No. of administered doses for all vaccines * 100 000. Through this value, we obtain the number of cases reported per 100 000 administered doses of vaccines in one year. The total doses of vaccines administered in one

year were available from 2006 to 2015. Using the vaccination coverage for each vaccine and the number of children and infants immunized with those vaccines we could calculate the total number of administered vaccine doses for the years 2003 to 2006. The AEFI rates were calculated with respect to vaccine type, age, sex, district, health outcome and seriousness. A series of regression analyses were conducted based on the findings from the descriptive-analytic study, to investigate risk factors differentiating serious and non-serious vaccine reactions, in terms of vaccine type, program factors, and socio-demographic factors. Both the relative effect size (as measured by OR and 95% confidence interval) and the p-value were examined to determine significance. Moreover, each event was evaluated about the quality and diagnostic certainty taking as reference the Brighton Collaboration Case Definitions for each AEFI.

RESULTS

Reported adverse events following immunization in Albania included encephalopathy, encephalitis, meningitis, convulsions, toxic shock, abscess, anaphylaxis, Bacillus Calmette Guerin (BCG) lymphadenitis, acute flaccid paralysis and fever. In total there were 464 vaccines reported as being related to the events and 11 types of vaccines.

Total number of AEFIs, vaccine administered and AEFI rate per years

During a thirteen year period (2003-2015) there have been 307 AEFI cases reported from immunization providers in Albania for a total of 7,713,325 doses of administered vaccines. As each case is characterized by more than one event reported, a total of 496 adverse events following immunization have been recorded. The mean reporting rate per year was 3.9/100,000 administered doses. There is an only one peak of AEFI rate which corresponds to the second year of AEFI surveillance system implementation in Albania. The rates of AEFI thereafter decrease significantly. In 2005 the addition of the parotid component to the MR vaccine introduced the trivalent vaccine Measles-Mumps-Rubella. During this year the AEFI rates were low but higher than the rates in the following years. The introduction of the Hib vaccine in 2009 leads to a slight increase in the rates of AEFI in 2010 which decrease again in 2011. However, the introduction of PCV vaccine in 2011 is reflected in an increase in rates of AEFI in the following year. The introduction of IPV vaccine in 2014 increases the rates of AEFI in this year and a similar rate is maintained also in 2015. The difference of AEFI rates throughout years was statistically significant ($p< 0.05$).

Distribution per gender

Gender was available in only 240 cases of which 106/240(44.2%) were females and 134/240(55.8%) were males. The ratio male; female has been almost constant throughout the years. There was no statistically significant difference between male: female ratio throughout years (Fisher's Exact test: 6.525, p=0.706)

Distribution per age classes

The variable age was grouped into 6 categories (Table 1). Most of the cases were recorded in infants aged < 4 months, 110 cases (35.8%), $p<0.05$. The difference in the proportion of cases for each category was statistically significant ($\chi^2=219$, $p<0.05$). In this study, the relationship between age and AEFI has been studied using Pearson's product moment correlation. Considering as zero hypothesis (H0) the theory according to which there is no correlation between age and AEFI we computed a statistical test using R software. We reject the respective H0 at a 5% level (p-value = 0.001123<5%), so the coefficient value (=0.1850745) is statistically significant. For greater ages (expressed in months in this case) there is a smaller probability to observe an AFEI event and vice versa.

TABLE 1. Age categories and frequency of AEFI cases in each category

Age category	Frequency of Cases	% of cases
<4	110	35.8%
4 - <6	78	25.4%
6 - <12	59	19.2%
12 - <18	8	2.6%
18 - <60	30	9.8%
≥60	22	7.1%
Total	307	100.0%

Distribution of AEFI and rate per single type of vaccine

In total there were 307 vaccines reported as being related to the events (Table 2). Because it was impossible to attribute the event/s to one of the vaccines, we attributed the event to each of the vaccines reported as previously administered by the infant.

The vaccines related to most of the cases was DTP and HepB

(38,3% of the cases). As these two vaccines were administered to the infant at the same sitting before 2009, they were reported together whenever an AEFI occurred.

The second most frequently reported vaccine was DTP (27,9% of the cases), followed by DTP-HepB-Hib(11.4%), DTP-HepB-Hib/PCV(8,4%), MMR(2,6%), DTP-HepB-Hib/IPV(2,3%). The vaccines for which there were less cases

reported were Td(1,3%), Dt(1,6%), TT(0,3%), dT(1,6) and PCV (1,3%).

TABLE 2. Vaccines reported as being related to the adverse events following immunization in Albania from 2003-2015.

Vaccines	Frequency	Percent
DT	5	1,6%
DTP-HepB-Hib	35	11,4%
DTP	86	27,9%
MMR	8	2,6%
Td	4	1,3%
DTP-HepB-Hib/PCV	26	8,4%
DTP/HepB	118	38,3%
DTP-HepB-Hib/IPV	7	2,3%
DTP-HepB-Hib/IPV/PCV	3	1,0%
Dt	5	1,6%
PCV	4	1,3
TT	1	,3%
dT	5	1,6%
Total	307	100,0%

Serious and not-Serious reactions

Most of the reported cases were non- serious (78,8%) compared with the serious ones (21,2%) ($p<0.05$). The ratio non serious; serious reactions is almost constant throughout years, (mean ratio; 4.2, p=0,018, 95% CI: 0,87-7,58) except in 2003 where this ratio is 21,50. In order to analyze the risk factors associated with a higher risk of serious vaccine reaction (compared to non-serious reaction), a series of multivariate logistic regression models were used. The factors considered for this analysis were grouped in socio-demographic factors (age, sex)) and program-related factors (vaccine type, dose number). The results of this analysis are shown in table 1. From the four factors considered for analysis, vaccine type could not be performed as the program considered it as an almost separated variable. While about age, dose number and sex it is observed that the odds ratio is not relevant and therefore none of this factors can be considered as a predictive one for developing serious reactions. 10.8% of the serious reactions were not healed at the moment of reporting compared with 2.1% of the non-serious category, (χ^2=10,33, p=.001). The relative risk of not healed cases was 5 times greater in the serious group compared with the non-serious group.

The relationship between time storage of the vaccine and the occurrence of adverse events

The stock time was grouped into three categories according to the relation between time and lipoligosaccarid (LOS) released from the vaccine. Most of these cases belonged to the category 1 (41/85, 48%), followed by category 2 (38/85, 44% of the cases) and finally category 3 (6/85, 7% of the cases) (Table 4). Pearson's product-moment correlation coefficient demonstrates that there is no relationship between variables 'stock time' and 'AEFI'. We accept the respective H0 at a 5% level (p-value = 0.25>5%), so the coefficient value (p=0.1259) is statistically not significant.

TABLE 3. The logistic regression analysis about factors that influence the occurrence of serious reactions

	Odds Ratio	95% CI	p
Age	1.0060	(0.9992, 1.0128)	0.093
Dose number	0.9635	(0.7472, 1.2425)	0.774
Sex	0.8250	(0.4738, 1.4365)	0.774

TABLE 4. The relation between stock time and frequency of AEFI

Stock time	Frequency	Percent
From 0-15 days	41	13,3
From 16-180 days	38	12,3
More than 180 days	6	1,9
Total	85	27,6

Program errors

The adverse events expected from programmatic errors include abscess at the site of injection, local reactions, sepsis, toxic shock syndrome, blood-borne syndrome, sciatic nerve damage or the vaccine might be ineffective. From the results obtained in this study, the following events might suggest a programmatic error: abscess (seven cases), toxic shock (two cases), local reactions (31 cases), and inflammation at the injection site (2 cases)

Districts

The cities with the highest reports are Lezha, Tirana, Lushnja, Peqin and Shkodra. While the cities with the lowest cases are Fier, Devoll, Libonik, Skrapar, Sarande, Vlore, Kruje. The difference between them was statistically significant ($p<0.0001$). The west regions of Albania are more aware of AEFI reporting system and the importance of reporting. While the southern regions are less aware.

Vaccination coverage

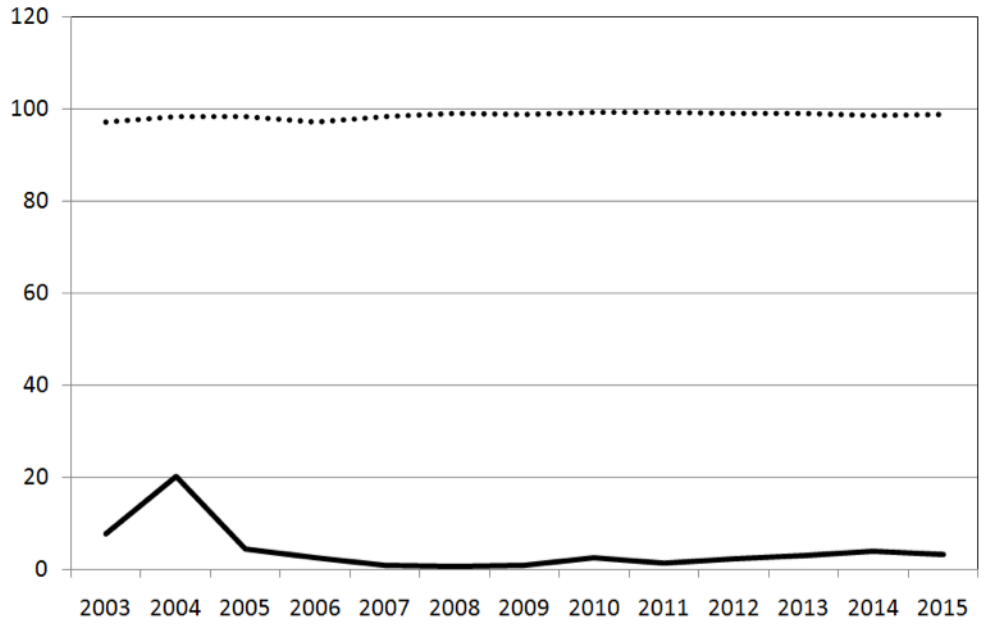
It is well known from the literature that whenever concerns about adverse events following immunization rise, the impact on vaccination coverage is significant. Starting from this theory it was attempted to analyze the correlation between this two variables in Albania. The figure 1 shows the temporal trend of vaccination coverage for all vaccines in Albania and AEFI rates for the period 2003-2015. From the figure, it can be observed that during the first years of the AEFI surveillance system functioning, the rates of AEFI were higher than in the following years while vaccination coverage slightly decreased. The statistical test used to analyze the correlation between these two variables was Pearson Correlation. There is a mild negative correlation between AEFI rates and vaccination coverage (r= -0.338) which means that whenever there is an increase in AEFI rates there will be a decrease in vaccination coverage. However, this correlation is not statistically significant (p=0.129).

DISCUSSION

Main results

From the analysis of the national AEFI database, it is concluded that the majority of the events reported during a 13 year period were mild and resolved without any sequel. There were no deaths reported and no other severe reactions which lead to the disability, the incapacity of the patient or into a congenital anomaly or birth defect. The incompleteness is noted in the demographic data in which in 67/307 cases gender information was missing. There were no gender-specific patterns or AEFI reporting rates. Clinical data show that males and females are different in their innate, humoral, and cell-mediated responses to viral vaccines, which may affect the frequency and severity of AEFI especially after viral vaccines [5]. Most of the cases corresponded to infants from birth to 4 months of age. This corresponds to the majority number of vaccines the child administers at this age compared with other ages. This result is confirmed also by the test used to assess the risk of developing AEFI in various ages who found a small strength of correlation between age and occurrence of AEFI. Theoretically, for a sensitive system, significant differences between geographic regions for vaccine reactions caused by the inherent properties of vaccine should not exist [6]. From the 36 districts of Albania, only 19 of them have reported AEFI during these 13 years. This is another indicator of underreporting. The awareness of health care workers and the strategy of the immunization program to enhance the reporting of AEFI are influenced by the setting area, mentality, the distance of this area from the capital and the perception of inhabitants about health. As it is noticed from the results the fluctuations of reporting rates throughout years reflect the changes that occurred into the immunization schedule for childhood vaccines. The

FIGURE 1. Temporal course of AEFI rates and vaccination coverage from 2003 to 2015



tendency to report any adverse event after the introduction of a new vaccine into the immunization schedule is known as the Webber effect [7]. From Pearson's correlation, the correlation between AEFI rates and vaccination coverage in this study is not statistically significant, although it suggests a mild negative association between these two variables. This result suggests that increased concerns about AEFI rates influence the vaccination coverage. The ratio of non-serious; serious reactions is almost constant throughout years, except in 2003 when the frequency of non-serious reactions significantly exceeds that of serious reactions. This is probably attributed to the fact that vaccine safety surveillance system was just introduced in Albania and immunization providers were unused and unaware of what should be reported. Socio- demographic factors such as age and gender and program related factors such as vaccine type and dose resulted to not be risk factors for serious reactions. Although data are not sufficient to confidently estimate the relation between stock time and AEFI, with the data available it can be suggested that stock time is well managed by vaccination officials at vaccination points but also at the Institute of Public Health. The majority of vaccines had a stock time less than 15 days. Therefore it can be concluded that the frequency of AEFI in Albania is not attributed to the long stock time. Programmatic errors which suggest for an inappropriate handling of immunization and vaccination practices were reported in a 13 year period. The worst of these events which might have a fatal outcome is the toxic shock syndrome which usually results from improper handling of vaccine vials once reconstituted. The two cases reported with toxic shock syndrome in Albania healed without problems and did not have any sequel. The same outcome was reported also for the 7 cases with an abscess. Programmatic errors can be prevented through proper staff training and an adequate supply of safe injection equipment [8].

Comparison with other similar studies

Albania is among countries which have low reporting rates. The mean annual reporting rate of 3.9/100,000 administered doses is close to the value of Switzerland [9] which reported a rate of 2,7/100,000 distributed doses. This value is too low compared with rates of Italy (12.5/100,000 administered doses [10]), Australia (12.5 /100,000 doses [11]), Zhejang Province of China (9.2/100,000 administered doses [12]), Cuba (57.8/100,000 administered doses [13]), Czech Republic (209/100,000 vaccine doses [14]), Spain (14,6/1000 vaccine doses [15]) and USA (11.4 /100,000 distributed doses [16]). Normal rates of the events depend from one setting to another and between countries and continents. Immunization policy and legislation modalities, vaccination programme policies, surveillance modalities, background epidemiology and incidence of the events in the population are all elements which differ from one country to another and which influence the rates of AEFI.

Serious events in Albania represented about 21% of all reported AEFI cases. This number was close to that of Switzerland which had the same percentage of serious events.

Countries which have problems with underreporting report high percentage of serious events as they tend to predominate over the total number of the events reported. Moreover the definition of serious events and what is considered a serious event, differs from country to country.

Strength and limitations of the study

This study includes all the cases reported from 2003-2015 in the Albanian AEFI database in which data are entered by professionals and bias regarding data quality are missing. However, the study is based on data reported passively by health care workers.

The limitations of passive surveillance of AEFI do not allow for meaningful interpretation and inference on the population about AEFI incidence due to underreporting. To complete the safety profile of each vaccine, additional methods are necessary.

Implication for the policy-maker

This is the first study of this type conducted in Albania and therefore it has a national relevance for understanding the development and evaluation of population-based AEFI post-marketing surveillance system and identifying the gaps to be filled, policies developed and the provisions undertaken needed to meet the WHO standards. This study gives way to further investigations about monitoring the vaccine safety in Albania.In order to standardize the "normal" rates of adverse events after immunization, all factors that influence these rates should be investigated. Therefore country-specific studies should be conducted in order to define "background rates" of the events and specify "what to expect". Whenever these studies are lacking, the only reference that can be used are the international values which in case of vaccine safety are pre-established by the World Health Organization.

In Albania, the Institute of Public Health and National AEFI committee are the two main organs responsible for performing causality assessment of AEFI. Despite the the function of this two organs, causality assessment is hardly performed in Albania.Causality assessment has been performed only for the serious events and it has been concluded that the events were not related to the previous vaccination. Causality assessment is performed by the National AEFI Committee based on the information gained by the investigation forms. The only tools used to get information

about an adverse event following immunization are the AEFI reporting forms and investigation forms. The investigation form is filled in by the District Directorate of Public Health within 7 days from the occurrence of the event. If laboratory testing is needed, the biological specimen or vaccine lot is forwarded at national level to the National Institute of Public Health. For serious cases, the investigation is performed immediately by the Institute of Public Health. Causality assessment is only done ,analyzing data collected. The responsible organs to perform causality assessment has not yet adopted the WHO algorithm for assessing the relation between a specific event and the previously administered vaccine. However it is difficult to establish an assessment of causality between the event and the previously administered vaccine due to the lack of data linkage.Moreover, increased awareness and trained staff to collect correctly and investigate the data is needed.

The completeness and accuracy of information in the Albanian vaccine safety surveillance system still need to improve. Due to the incompleteness of the data, it could not be concluded about any specific relationship between AEFI and factors related to them.

Key points

- The majority of the events reported during a 13 year period are mild and resolved without any sequel;
- There were no gender-specific patterns of AEFI or gender-specific reporting rates;
- Most of the adverse events were reported in infants from birth to 4 months of age;
- There was a statistically significant difference between various districts regarding the AEFI reporting rates;
- The completeness and accuracy of information in the Albanian vaccine safety surveillance system still needs to improve.

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Source

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