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Prevention and monitoring of adverse events following immunization: the "Green Channel" of the Veneto region in Italy

G. Zanoni [a,*], T.M.D. Nguyen [a,b], M. Valsecchi [b], G. Gallo [c], G. Tridente [a]

[a] *Immunology Unit, Department of Pathology, University of Verona, Policlinico G.B. Rossi, 37134 Verona, Italy*
[b] *Local Health Unit No. 20, Department of Prevention, Via S. D'Acquisto No. 7, 37122 Verona, Italy*
[c] *Regional Health Authority, Dorsoduro 3493, 30100 Venezia, Italy*

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Abstract

Measures to improve vaccine safety are essential for successful immunization programs. Therefore, an activity for vaccine adverse events prevention and surveillance, named the Green Channel, was established in the Veneto ion of Italy in 1992. This report summarizes the results of 10 years activity of a specialized pre-vaccination counseling service, offered to 543 selected at risk individuals referred for prior AEFIs or suspected contraindications (CI) to vaccine administration. Furthermore, data on 1762 AEFIs reported in this region are analyzed and discussed. This joint activity appeared effective and it is proposed as a model.

Keywords: Immunization; Adverse events; Surveillance

1. Introduction

Vaccines are the most effective tools in preventing infectious diseases. However, immunization, like any other medical intervention, may cause adverse events, usually mild to currently available vaccines, occasionally severe [1]. Accurate anamnesis, prior to vaccination, reduces such risk by picking up subjects with temporary or permanent contraindications (CI) [2]. Laboratory mass screening is useless and unethical under these circumstances. However, specific procedures for selected cases are useful to better assess the existence of CI and administer vaccines in safer conditions [3,4].

Since the safety demand at individual level is growing, particularly in areas where vaccine preventable diseases are uncommon [5], many countries are experiencing different models of adverse events following immunization (AEFIs) surveillance and prevention systems [6].

In 1993, the Veneto Region Health Authority was asked to support a special service for prevention, evaluation, and monitoring of AEFIs, named the Green Channel [7], proposed by the Institute of Immunology and Infectious Diseases at the University of Verona, now Immunology Unit, at the Department of Pathology, with the following tasks:

1. A specialized pre-vaccination counseling service, for the Local Health Units (LHUs), to evaluate the suitability to vaccination of subjects with history of previous AEFI or CI;
2. A wire consultation service (telephone, fax, e-mail), for LHU personnel and citizens, on general issues or specific cases regarding AFFIs and CI;
3. A validation system for AEFIs within the Veneto Region, analyzed and classified by dedicated immunologists, and periodically returned to the LHUs and to the Public Health Authorities, with due commentary.

This report summarizes the overall activity of a 10-year period, supplied by the Green Channel, with the aim of offering a model of organization at regional/national level for surveillance and prevention of AEFIs which, to our experience, has proved to be easily manageable and efficient.

2. Methods

2.1. Organization of the Green Channel counseling activity

A preliminary start up during 1992 was set only for the province of Verona. After 1 year, on the basis of the results communicated to the Veneto Health Authority, the service was proposed and approved for extension to the whole

* Corresponding author. Tel.: +39-045-8074256; fax: +39-045-580900.
E-mail address: giovanna.zanoni@univr.it (G. Zanoni).

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region, whose population accounts for 4.5 million inhabitants with about 43,000 newborns per year. The service was initially operated on a voluntary basis by one academic immunologist and one specialist in allergy and clinical immunology. Starting from 1994, the service received additional support from one part time fellow specialist (either allergist or public health physician). The administrative support was given by the staff of the Immunology Unit. The Veneto Region supported the service with a grant for the fellowship and general expenses. The Green Channel was mainly aimed at preventing adverse reactions in subjects who required a special examination for presumed AEFI or CI to start or continue vaccine administration, and to give correct information on vaccine risk/benefits to non specialists and citizens. Later on, the Region provided the service with AEFI reports for validation, classification and asked for periodical information to all LHU personnel. Before starting with the enlarged regional service, the Immunology University Institute and the Veneto Public Health Authority organized an itinerant course for LHU personnel to present the project and fresh up the immunological basis of modern vaccination, the risk/benefit evaluation, the importance of timely notification of AEFIs and the strategies of the network intended to establish among the LHUs and the Green Channel service. A standardized anamnestic questionnaire was introduced at LHU level to rule out any CI before admitting children to vaccination. When requested by LHU officials, the Green Channel was alerted on specific issues. Here, the case analysis consisted on clinical and/or accurate records' examination, with an in-depth family and individual anamnesis, to evaluate prior AEFIs and underlying pathologies as potential risk factors. When indicated, further clinical, in vivo and in vitro tests were performed, also using vaccines or their components, in order to identify specific sensitizations. Eventually, specialists from other disciplines were consulted to formulate joint opinions and/or agree on targeted clinical and laboratory testing. Finally, a conclusive report was released, containing instructions for vaccination to LHU (i.e. standard procedure, pre-medication, temporally separated single injections, hospitalization, different vaccine preparation, temporary suspension, exemption).

2.1.1. Wire consultation

This activity was initially carried biweekly by telephone in response to general or specific questions on CI and AEFIs. Consultations were provided primarily to LHU professionals, but also to attending/hospital physicians and to citizens. The service is now active by e-mail and fax.

2.2. AFFI Surveillance

A Regional Monitoring System integrated the Green Channel activity for AEFIs starting from 1993, to the responsibility of the Immunology Section at the University of Verona, to cooperate also with the National Surveillance System and ensure a regular return of data to the health care professionals.

The notification of AEFIs is mandatory in Italy; a national injury compensation system was established in 1992. The AEFI report form, published by the Ministry of Health, also provides case definitions of serious conditions. These reports were sent by the LHUs to the Regional Health Authority, and then forwarded both to the Ministry of Health and, to this Immunology Unit. Here the forms were examined, classified and computerized into Epi-Info database. Unusual and serious cases were thoroughly studied and followed, up to recovery or stabilization of the lesion. When requested, additional instructions for case handling was provided.

The existence of a causal relationship was classified according to WHO causality score as: *definite*, *probable*, *possible*, *unlikely* and *unrelated* in analogy to terminology adopted for pharmacovigilance, subsequently adopted for vaccine surveillance [8]. When essential data were incomplete, the case was defined as *unclassifiable*.

Case inclusion in the above mentioned categories was determined by a score system mostly accredited by the scientific community [8–11], based on four major criteria (three for case inclusion and one for exclusion):

- temporal relationship compatible with the event;
- biological plausibility, i.e. an event explainable by the biological properties of the vaccine;
- statistics/epidemiology, i.e. validation by comparison with data from vaccine safety studies;
- discovery of alternative causes of the event such as drug administration, underlying disease), and 12 minor criteria (11 for case inclusion 1 for coincidental non-related event):
- clinical: individual pre-disposition, history, previous AEFI, cross-reactivity, latent disease triggered by vaccination, physical examination, diagnostic tests, laboratory data, imaging, response to therapy;
- bibliographic: from related case series and reports;
- identification of other causal or triggering conditions not related to the vaccine.

In particular, a *definite* correlation assignment was given by scoring either three major criteria or two major and two minor, *probable* assignment would score two major or one major plus three minor; *possible* assignment required one major plus two minor, or five minor criteria, *unlikely* scoring less than previous categories and *unrelated* showing evidence of other etiological causes or trigger factors not due to vaccine administration.

Reports causally related to vaccination were also classified as to their seriousness into *common*, *relevant* (clinically significant although resolved spontaneously or with treatment within a few hours or days), and *serious*, as defined by the onset of life-threatening reactions, residual disability, neurological symptoms, hospitalization, or death.

The entire activity is summarized in Fig. 1.

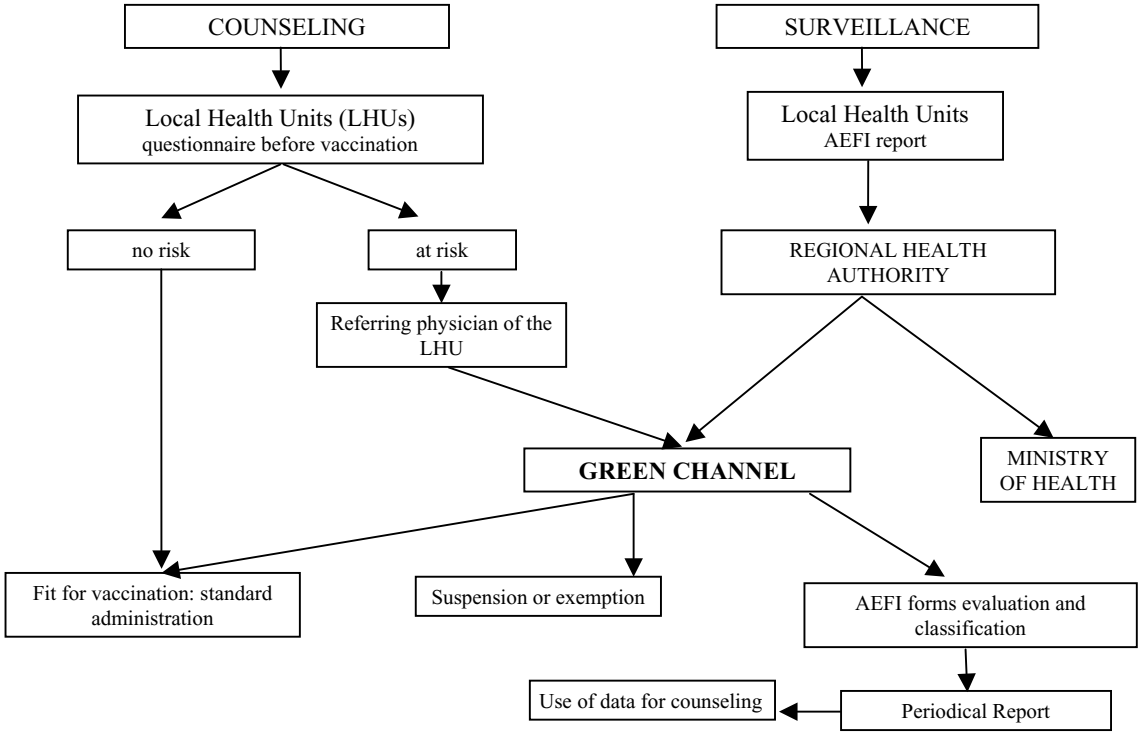

Fig. 1. Veneto network organization. Vaccination counseling and surveillance activity.

2.3. Periodical reports

Four official reports on the overall activity of the Green Channel were prepared by the specialists of the service and forwarded to the Public Health Authorities and to the referring physicians of the LHUs.

They included the classification of consultations grouped in the following major categories: type of inquiry, number of pediatric and adult cases with an arbitrary shift at 13 years of age, to include all the school-age vaccinations with mandatory hepatitis B (HB) immunization of 12 year olds[1], type of vaccine, manifestations and causality of AEFI, nature of suspected CI referred, advice given by the Service, number and type of vaccines administered after the counseling.

The AEFI notifications included: LHU reporting the AEFI, vaccines administered, age of the subject, number of doses, time interval between administration and the onset of the reaction, nature of the reaction, responsible vaccine (if identified) when more than one vaccine was administered, extent (local injection site versus systemic reactions), seriousness and causality score.

The fourth report summarizes and comments the data of the period 1993–1999 and is now available on the web site of the Immunology Section (http://www.med.univr.it/immunol). Surveillance data of the period 2000–2001 are now on analysis to be included in the fifth report on the Green Channel activity, part of which are anticipated in the present report.

[1] The Italian law no. 165/1991 introduced as mandatory the HB vaccination for infants and 12-year-old children.

3. Results

3.1. Green Channel pre-vaccination consultations

In the 1992–2001 10-year period, a total of 543 patients referred to the Green Channel; children up to 13-year old represented 77% of the whole cases. Direct clinical examination by the specialists of the service was done in 51% of cases, while in 49% the consultation was based on records' review.

The referrals to the Green Channel were divided into two main categories: previous AEFIs, as for 241 (44%) cases, and CI assessment for 302 (56%), as listed in Table 1. Obviously, in a number of cases, multiple and complex inquiries were posed for the same individual regarding both categories.

The reported AEFIs (Table 1, A) to previous administrations followed the vaccines administered in the first year of age in 87 (36%) cases, with systemic manifestations; 83 (34%) AEFIs were related to HB vaccine and 44 (18%) were due to toxoid boosters, with injection site and systemic reactions. The remaining inquiries were done for AEFIs related to OPV in 9 (3.7%) cases, MMR for 5 (2%) subjects, and other vaccines in 13 (5.3%) cases. As regards the nature of the AEFI, skin manifestations were the most frequent reactions; suspected neurologic events after vaccination were referred in 26 cases, with a causal correlation in 14 of them. Shock-collapse or hypotonic-hyporesponsive episodes (HHE) [8] were reported in 21 children given various vaccine combinations, with pertussis vaccine in most

Table 1
Referral to the Consultation Service

Previous AFFI	Vaccines associated with event						
	First year series[a]	HB[b]	DT/TT booster	OPV	MMR	Other vaccine[c]	Total (%)
(A)							
Injection site reaction	0	5	15	0	0	1	21 (9)
Systemic event							
Skin manifestation	32	38	15	2	2	6	95 (39)
Neurologic symptoms[d]	13	5	2	4	1	1	26 (11)
Shock-collapse or hypotonic-hyporesponsive episode	18	0	0	1	0	2	21 (9)
Fever + other mild symptoms	11	4	2	0	1	0	18 (7)
Vaccine hypersensitivity[e]	1	6	4	0	0	1	12 (5)
Respiratory symptoms	4	4	2	0	0	1	11(4)
Cephalalgia	0	7	1	0	0	0	8 (3)
Arthralgia/arthritis	0	5	0	0	0	0	5 (2)
Thrombocytopenia	2	0	1	0	0	0	3 (1)
Other events	6	9	2	2	1	1	21 (9)
Subtotal	87	83	44	9	5	13	241 (100)
Suspected contraindication	Vaccines to be administered						
	First year series[a]	HB	DT/TT booster	OPV/IPV	MMR	Other vaccine[c]	Total (%)
(B)							
Allergic disease	6	42	1	0	0	2	51 (17)
Neurologic disease	15	13	1	5	10	2	46 (15)
Vaccine hypersensitivity[e]	0	12	1	0	3	12	28 (9)
Immunodeficiency	12	2	1	7	1	1	24 (8)
Autoimmune disease	3	13	1	1	4	1	23 (8)
Congenital disease	4	1	0	2	0	2	9 (3)
Migraine	0	8	0	0	0	0	8 (3)
Drug allergy	0	3	1	0	1	0	5 (1)
Chronic urticaria	1	2	1	0	0	1	5 (1)
Reactions to other vaccines	0	4	2	0	1	0	7 (3)
Miscellaneous	5	9	1	0	0	8	23 (8)
Family history of AEFI	8	7	0	11	0	0	26 (9)
Family history of diseases[f]	6	5	0	1	1	1	14 (5)
Fear of risk of AEFIs[g]	25	7	1	0	0	0	33 (11)
Subtotal	85	128	11	27	21	30	302 (100)
Total	172	211	55	36	26	43	543

DT: Diphtheria–tetanus vaccine; TT: tetanus vaccine; OPV: oral polio vaccine; HB: hepatitis B vaccine; MMR: measles–mumps–rubella vaccine.

[a] First year series: one or more mandatory/recommended vaccines administered in the first year of age (diphtheria–tetanus–pertussis whole cell vaccine/acellular pertussis vaccine, *Haemophilus influenzae* type B vaccine, HB, oral or inactivated polio vaccine).

[b] Four in co-administration with rubella or TT.

[c] Other vaccines: influenza, yellow fever, tuberculosis vaccine, hepatitis A vaccine, *Haemophilus influenzae* type B vaccine, varicella vaccine.

[d] Neurologic symptoms: seven encephalopathies, four motor alterations, three facial palsy, three strabismus, two neuritis, one convulsion, one ataxia, one GBS, one VAPP, one paresis, one myelitis, one tic.

[e] To the vaccine or its component (i.e. preservative, contaminant, adjuvant).

[f] Severe allergic diseases, immunodeficiency, neurologic disorders.

[g] Including HLA "at risk" as false contraindication stated from one private physician.

of them; another group of 21 subjects was referred for injection site reactions. Other AEFIs submitted included 18 cases of fever plus other mild symptoms, 12 cases of hypersensitivity to vaccine components, 11 respiratory symptoms, and 8 and 5 cases of cephalalgia and articular symptoms, respectively, all but one related to HB vaccine. Three cases of thrombocytopenia were also evaluated. The causality score assessed in the 241 AEFIs was judged as definite in 14.5%, probable in 50% and possible in 21% of cases. In 14.5% of consultations, the referred AEFI appeared unrelated.

Table 1, B reports data on 302 presumed CI submitted to the Green Channel. The majority (128 cases, 42%) refers to HB vaccine administration; a second consistent group refers to the first year vaccine series administration (85–28%), 27 (9%) were sent for polio immunization, 21 (7%) for MMR and 11 (3.6%) subjects were referred for toxoids administration. Allergic, neurologic and immune system underlying disorders were the most frequent reasons submitted as CI. Fourteen cases were referred for a family history of AEFIs or chronic diseases and 33 for fear of risk of AEFIs; 30 of these

were based on HLA haplotype check considered to be "at risk" by an external private consulting surgeon (see below).

Of the all 302 suspected CI, once evaluated, 159 (53%) were judged as plausible. They included immunodeficiency, hypersensitivity to vaccine components, active autoimmune disease, undiagnosed neurological illness. For the major part of these cases vaccination was advised indicating the precautions to be adopted.

The final advice on the 543 submitted cases was given as follows: vaccination was indicated in 389 cases (72%), suggesting precautions in 188 of them (protected environment, pre-medication, or different vaccine preparation, or temporally separated single injections).

Temporary suspension or exemption was requested in 52 (10%) and 48 (9%) cases, respectively, due to serious AEFI to earlier doses or consistent CI for individual vaccines. Thirty-six (6.6%) were advised for further testing before final reporting. However, some of them opted not to perform. A group of 18 (3.4%) was given other advice (on causal relation, immunization not due, etc.).

The vaccination was actually administered to 258 (66%) subjects judged suitable to start or continue the immunization (Table 2). In particular, 142 with suspected CI and 116 with previous AEFI were vaccinated after consultation; the latter followed a standard procedure in 42 cases, 31 underwent temporally separated single injections and/or pertussis vaccine suspension, 21 were hospitalized for vaccine administration, 11 needed pre-medication and 11 received a different vaccine preparation. Only common mild and short lasting adverse effects were observed in 10 subjects.

A total of 61 cases refused to continue the vaccination: they included the most part of subjects submitted to the Green Channel after the HLA typing advised by a private consultant. After repeated similar requests Health Authorities were asked, both at regional and national level, for an official position, to reject the issue as a non evidence-based individual statement. In other 52 patients with a Green Channel positive advice the vaccination was postponed or not done, due to public health physician's decision. Feed back data on vaccine administration after counseling are missing for 18 subjects.

Table 2
Vaccines administered after evaluation by the Green Channel

Vaccines administered	Number	AEFIs (no. of subjects)
HB/HA	93	Fever + arthralgia (1)
DT ± Pw/aP ± others[a]	87	Irritability (2), injection site reaction (1), dermatitis (2)
DT/TT booster	31	Faintness (1), dermatitis (1)
Yellow fever	15	0
Polio	18	0
MMR	11	Fever (1), dermatitis (1), rash (1), lymphadenopathy (1)
Influenza	3	0
Total	258	

[a] First year series.

Wire consultations were asked for 2210 cases and 370 general issues for a total number of 1869 calls. The principal users were LHU operators (70%), followed by pediatricians, general practitioners or other specialists (18%), and with increasing frequency, citizens (12%). Wire counseling was also required for patients living in distant provinces and for urgent cases like scheduling errors or recent exposures to infectious diseases preventable by active or passive immunization. Among general questions, information was mostly asked for: association between autoimmune diseases and the risk of administering vaccines; Kawasaki disease and vaccinations; use of live vaccines during pregnancy; hepatitis A and malaria prevention: neurologic disorders which could contraindicate immunization; potential risks deriving from the use of mercurial preservatives.

3.2. AEFI surveillance

In the period 1993–1999, 1762 report sheets were evaluated and classified. These cases include only part of AEFI resulting from the pre-vaccination inquiries because of the different time of observation.

Classification of data by type of vaccine administered is shown in Table 3. More than one vaccine was given simultaneously in 503 (29%) reports. The highest AEFI frequencies were observed for diphtheria–tetanus (DT) and tetanus toxoid (TT) vaccinations, followed by co-administered DT–pertussis whole cell (Pw), oral polio (OPV) and HB vaccines.

The distribution of reports by age groups, when reported, indicated that 37% of events occurred among adolescents and adults (>13 years) and 26% in children <1 year of age. An additional 18% was observed in the 1–5 years of age group and 18% in the 6–13 age group. As for time of onset of symptoms, 63% of the reports concerned events that appeared within 24 h after administration and 28% fell in the 1–7 days interval; only 7% of AEFIs was reported more than 7 days after the vaccine administration. By examining the degree of causality, it was found that 1705 reports (96.7%) were related to the vaccination with various degrees of causality: definite (77%) probable (18%), and possible (1.5%). The 3% of AEFIs were judged unrelated and an additional 0.3% was unclassifiable for essential data missing. The nature of the AEFIs, classified only in reports causally related to the vaccination, is listed in Table 4. Only in the case of toxoids, the frequency of injection site reactions reached 58%.

The 1705 cases of causally related manifestations (96.7%) were subdivided on the basis of the degree of seriousness into common (1365—80%), relevant (254—15%), and serious (86—5%). All serious events were evaluated through complete records' examination and information given by the referring physician or pediatrician and followed up to recovery or stabilization of the lesion. They include 26 local reactions (abscesses) classified as definite, and 60 systemic

Table 3
Distribution of reports by vaccine administered

Vaccine	Number (%)
DT	325 (18.5)
TT	316 (18)
DTw + OPV + HB[a]	265 (15)
HB	237 (13)
MMR	86 (4.8)
Influenza	81 (4.6)
DtaP + OPV + HB	77 (4)
DTPw	47 (2.7)
DtaP	41 (2.3)
Hib	30 (1.7)
Live typhoid	24 (1.3)
Measles	17 (0.9)
BCG	15 (0.8)
HB + MMR	14 (0.7)
DtaPHB + OPV	12 (0.6)
DT + MMR	9 (0.5)
DtaP + MMR	8 (0.45)
DtaP + OPV + HB + Hib	8 (0.45)
DT + OPV + HB	8 (0.45)
OPV	8 (0.45)
DtaPHB + IPV	7 (0.4)
Rubella	7 (0.4)
HB + TT	6 (0.3)
MMR + Hib	6 (0.3)
Rubella + HB	6 (0.3)
DTP + HB	6 (0.3)
DTP + OPV	6 (0.3)
DT + HB	6 (0.3)
DTaPHB	5 (0.28)
DT + aP + HB + OPV	5 (0.28)
Other single or combined[b]	74 (4.2)
Total	1762 (100)

DT: diphtheria–tetanus vaccine; TT: tetanus vaccine; DTPw: diphtheria–tetanus–pertussis whole cell vaccine; OPV: oral polio vaccine; HB: hepatitis B vaccine; MMR: measles–mumps–rubella vaccine; DTaP: diphtheria–tetanus–acellular pertussis vaccine; Hib: *Haemophilus influenzae* type B vaccine. BCG: tuberculosis vaccine; DTaPHB: diphtheria–tetanus–acellular pertussis–hepatitis B vaccine; aP: acellular pertussis vaccine.

[a] In the period 1993–1996.

[b] One or more vaccines with <5 frequency.

Table 4
Nature of events related to the vaccination[a]

Vaccine adverse events	Number
Injection site reaction	1012
Systemic reactions	2382
Fever ≤39 °C	400
Fever >39 °C	192
Cephalalgia	131
Persistent crying	128
Urticaria/angioedema	126
Muscle weakness	111
Arthralgia	106
Pruritus	99
Exanthema	98
Irritability	90
Hypotonic-hyporesponsive episode	68
Vomiting	66
Breathing difficult	64
Anorexia	61
Pallor	54
Diarrhoea	48
Nausea	41
Gastrointestinal pain	33
Erythema	30
Parotid enlargement	28
Dizziness	26
Malaise	25
Pain	25
Cyanosis	24
Lymphadenopathy	24
Dermatitis	22
Torpor	19
Pharyngeal hyperaemia[b]	19
Fever convulsions	18
Somnolence	17
Tremor	15
Paraesthesia	13
Faintness	11
Hypotension	10
Conjunctivitis	10
Arrhythmia	9
Myalgia	8
Constipation	7
Hypertonia	7
Insomnia	7
Convulsions	6
Coughing	6
Encephalic signs	5
Glottic oedema	5
Ataxia	4
Encephalopathy	4
Thrombocytopenia	4
Anaphylactic shock	3
Confusional state	3
Skin vasculitis	3
Erythema multiforme	3
Dysphagia	3
Facial palsy	3
Aseptic meningitis	2
Meningism	2
Subicterus[b]	2
Tonic-clonic contractions	2
Petechiae	2
Myopathy	2
Henoch-Schonlein purpura	1
Serum sickness	1
Left cardiac failure	1
Strabismus	1
Hepatomegaly	1
Guillain-Barrè syndrome	1
Hepatitis	1
Venous thrombosis	1
Breath-holding spells[b]	1
Hyperbilirubinaemia	1
Transient paresis	1
Myelitis	1
Hearing decreased	1
Miscellaneous[c]	11
Total	3394

[a] In 1705 forms; unrelated and unclassified reports are not included.

[b] As reported by the physician, not included in WHO preferred term.

[c] Not serious events with <5 frequency.

reactions, of which 19 definite, 32 probable, 9 possible. They all recovered completely except for seven neurologic cases, five of which are still presenting sequelae, and two are still undergoing treatment.

4. Discussion

Vaccine safety is an essential issue both for citizens and health care personnel. Measures to prevent and control AEFIs are critical for successful immunization programs [8]. Therefore, effective monitoring systems, aimed to collect adverse effects and to distinguish true vaccine adverse reactions from coincidental events, are important for checking for rare or unusual reactions to new vaccines rarely assessed during pre-licensing studies [12,13]. USA, Canada, The Netherlands and Italy, are particularly active in this field [14–17,7]; other countries are revisiting their own procedures. CDC is also considering the establishment of Clinical Immunization Safety Assessment Centers to better reach these goals (see http://www.cdc.gov/programs/).

Other countries experienced the value of a special service to deal with children at risk for vaccination. In two reports concerning vaccination of children in the presence of clinical uncertainties or fears, or with a past history of AEFI vaccine administration proved to be safe with the support of special immunization services. Therefore, it was suggested that such activity should be part of an immunization program [3,4].

Following these lines, to better improve the work on AEFI prevention and surveillance, and also in response to anti-vaccine movements irrational campaigning in our country, this activity started in 1992 and is currently operating in the Veneto region. The consulting activity allowed the evaluation of 543 individuals at risk of AEFI. Referrals for suspected CI (56%) predominate over those on prior AEFI (44%).

From the entire study population, it appears that for the majority of the subjects evaluated (72%), the suggested vaccination procedure was found in a favorable risk/benefit ratio; in particular 66% of these were effectively vaccinated under standard or protected conditions. Only subjects for whom the vaccination could represent a risk that outweighed the benefits deriving from the complete protection or resulted temporary unnecessary were temporally suspended from the vaccination (10%) or exempted (9%). The wire consultations were particularly useful for subjects living in distant areas and for urgent cases.

The Veneto region AEFIs surveillance system was intended to integrate the national surveillance system, whose last published data showed that the reporting rate in our region is among the highest of the country [18], although a margin of underreporting and biased reporting, with considerable differences between different LHUs, must still be taken into account. We believe that the counseling and surveillance activity contributed to the growth both of compliance and vigilance on vaccination procedures.

At the beginning, local AEFI reporting was encouraged also for common events, in order to improve the attitude to report avoiding data missing. The collected data showed that the most frequent AEFIs derived from diphtheria and tetanus toxoids, with injection site reactions in 58% of reports: we believe that most of these events are probably due to excessive boosters, since the same evidence came from the cases referred for consultation. Therefore, in such experience, we recommended to check the level of circulating anti-toxin before administering further doses. A high number of reactions to co-administered vaccines in the first year of life were found associated to the DTPw used in the past (18.3%). The reactions to acellular pertussis vaccine included in the various formulations were less frequent (8.8%), in agreement with published data [19,20].

As for the serious AEFIs reported, the majority completely recovered, even in the presence of neurologic manifestations (51/86). The frequency of sequelae was 0.3%; cases still undergoing treatment accounted for 0.1%. However, it should be emphasized that in only one-third of these cases, it was possible to establish a high degree of causal relationship. We calculated an overall frequency of 1.7–3.4 reports/10,000 doses per year administered.

At the national level, on a total of 657 AEFIs reported in 1996, 0.3% cases manifested sequelae and 0.6% were in treatment at the time of the notification [18].

The overall degree of causality found in the Veneto reports showed a good capability of health care personnel in identifying causally related reactions (97%) and physicians particularly skilled in vaccine safety appreciated to receive a timely periodical report of the data with commentary from the immunologists of the service.

The regional (local) AEFI collection and assessment seems to be more affordable, compared to a central (national) monitoring system at least for this country, since the closeness to the single cases allows a more rapid check of correlations, direct observation of lesions, and eventually proceeding with appropriate diagnostic procedures for etiological identification and differential diagnosis in due time. However, the most important aspect of this model is the introduction of a preventive control on selected subjects, together with AEFI detection system. This aspect has produced at least two positive effects: the possibility of following individual cases at risk in a preferential “personal line” without disturbing the mass vaccination system; the significant impact on compliance to vaccination, by offering such service to single individuals, at risk or simply worried by mandatory administration of vaccines based on mass statistical low levels of risk. On this aspect, it seems to us very important that the preventive service and the post-detection of AEFI is to be activated in the same local organization, where experts have direct and prompt access to AEFI data as a source of information, when they examine single conditions at risk or give advice to people to be vaccinated and their families.

Similarly, full explanation on the uselessness of immunological preventive "check ups" and direct information on precautions to be adopted for individual cases (i.e. single administration of vaccines, pre-medication, day hospital, etc.), has produced optimal feed-backs, allowing vaccination of subjects who could have been incorrectly exempted.

Finally, another advantage of such a network resides in the possibility of offering to new incoming vaccines a highly affordable post-marketing surveillance system operated by the same experts that collect and evaluate AEFI reports. In fact, the double-arm of this model may be critical either for selection of the population samples to be employed and for a correct follow of AEFIs compared to adverse events observed in the same area for other vaccines.

In conclusion, the activity performed in these 10 years by the Green Channel, has proved to be manageable, easily expandable from local to wider areas by gradual settings of integrated small nets (regional; 5–6 millions people each).

We believe, therefore, the model can be proposed to others' evaluation and experience.

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