

The “Green Channel” of the Veneto region as a model for vaccine safety monitoring in Italy

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Abstract

Modern vaccinology and public health organizations need to satisfy an increased safety demand. Therefore, to improve adverse events following immunization (AEFIs) surveillance systems, some countries have established clinical evaluation centers for AEFI assessment and management of at risk individuals. In the Veneto region of Italy, the Green Channel operates through a counselling service for subjects with prior AEFI or with suspected contraindications to vaccine administration, and a surveillance system of the AEFIs reported in the region. Updated data on 753 consultations and 3023 AEFI analyses are discussed together with the opportunity to include the Green Channel model as part of an international vaccine safety network.

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1. Introduction

Modern vaccinology has led to develop new highly immunogenic and safe instruments against infectious diseases [1]. However, the safety demand has increased, along with the contribution of misinformation and the increased popularity of anti-vaccine movements, particularly in areas where vaccine preventable diseases are uncommon [2]. Although serious adverse events following immunization (AEFIs) are rare, it is sometimes difficult to ascertain a causal association and establish eligibility for further administration at the individual level. For this reason some countries are improving their surveillance systems establishing clinical evaluation centers for AEFIs [3].

In 1993, the Veneto Region Public Health Authority approved a project for vaccination improvement, which established a special service for prevention, evaluation, and monitoring of AEFIs, named the Green Channel [4], at the Immunology Unit of the Department of Pathology, at the University of Verona. The Green Channel had the following tasks:

- (1) a specialized pre-vaccination counselling service, for the Local Health Units (LHUs), to evaluate the eligibility to vaccination of subjects with the history of previous AEFI or contraindication (CI);
- (2) a surveillance system for AEFIs reported in the Veneto region, analyzed, classified and published in periodic reports for the LHU officials.

This report updates the overall activity supplied by the Green Channel, described in detail in a previous publication [4], and anticipates the converging efforts for international collaboration in this field [5].

2. Methods

2.1. The Green Channel counselling activity

The pre-vaccination counselling was addressed to subjects who needed a special examination for presumed AEFI or CI to start or continue vaccine administration, raised from a standardized anamnesis used at LHU level to rule out any CI before vaccination. When requested by LHU officials, the

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Green Channel was alerted on specific cases. Here, prior AEFI and/or underlying pathology as potential risk factor was evaluated by clinical and/or accurate record's examination, an in-depth family and individual anamnesis, and, eventually, specialistic consultation from other disciplines and in vivo/in vitro tests, in order to identify specific sensitizations. Finally, a conclusive report was released to LHU, containing instructions for vaccination with standard procedure or precautions (i.e. pre-medication, temporally separated single injections, hospitalization, different vaccine preparation), or, in selected cases, indicating temporary suspension or exemption.

A wire consultation service (telephone, fax, e-mail), on general issues or specific cases regarding AEFIs and CI was also available for urgent or simple questions and for risk communication.

2.2. AEFI surveillance

A Regional Surveillance System for AEFIs reported in the Veneto region was also commissioned to the Immunology Section of the University of Verona, to cooperate also with the National Surveillance System. Details regarding the notification of AEFIs in Italy and regional surveillance activities are included in a previous article [4].

The AEFI reports sent to this Immunology Unit were examined, classified and computerized into a specific database. Unusual and serious cases were thoroughly studied and followed up to recovery or stabilization of the lesion. Data were classified according to 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, system organ classes, extent (local injection site versus systemic reactions), seriousness and degree of causality (*definite, probable, possible, unrelated* and *unclassifiable*) adopted for vaccine surveillance [6].

Reports causally related to vaccination were 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.

During the overall period, six official reports on the counselling and surveillance activity of the Green Channel were prepared by the specialists of the service and forwarded to the public health authorities and the referring physicians of the LHUs.

3. Results

3.1. Pre-vaccination consultations

A total of 753 patients, with 80% children, were referred to the Green Channel in the 1992–2003 period. Evaluation

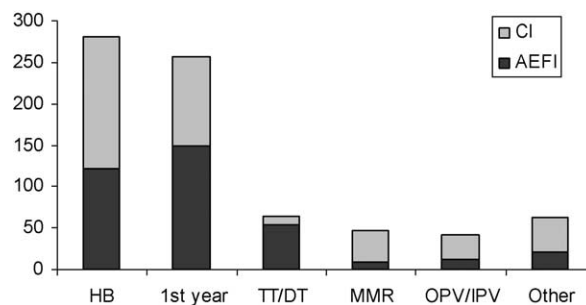


Fig. 1. Vaccines involved in the referrals (1st year series: one or more vaccines administered in children aged <1 year; Other: influenza, yellow fever, varicella, BCG, hepatitis A vaccine).

for the previous AEFI was done in 368 (49%) cases, and CI assessment in 385 (51%). Allergologic tests with vaccines and their components were performed in 166 (22%) of the subjects.

The vaccines involved in the referrals, requested for previous AEFI or suspected CI, are shown in Fig. 1; mandatory HB vaccine was implicated in 281 (37%) evaluations, followed by the vaccines administered in the first year of age in 257 (34%) cases. The remaining consultations were done for toxoid boosters, MMR, polio vaccines and others.

The clinical data submitted to the counselling service are reported in Table 1. The type of previous AEFI included local and systemic events; the most frequently referred were skin manifestations. After the evaluation, the reported AEFIs appeared unrelated to vaccines in 14% of the consultations.

A personal history of neurologic, allergic and immune system underlying disorders were the most frequent reasons submitted as CI. A family history of serious AEFIs or underlying disease in 47 cases implied the need of correct risk/benefit communication to the parents. The 47% of the suspected CI, once evaluated, were judged as false and the immunization was consequently advised.

Overall, vaccination was indicated in 555/753 cases (73%), suggesting precautions in 244 of them (protected environment, pre-medication, alternative formulation, or single administration), temporary suspension or exemption was requested in 69 (9%) and 60 (8%) cases, respectively, due to consistent CI to individual vaccines or severe AEFI to earlier doses. Forty-four (6%) were advised for further testing before final reporting. However, some of them refused such advice. A group of 25 (4%) was given other advice (on causal relation, immunization not due, etc.).

The vaccination was actually administered to 378 (68%) subjects, of which only 23 of them (6%) showed mild and short lasting adverse effects. A total of 71 cases refused to continue the advised vaccination. In other 43 patients the vaccination was postponed or not done, due to public health physician's decision. Information regarding vaccine administration after counselling is missing for 63 subjects (17%).

Table 1
Clinical data submitted to the Consultation Service

	Number of cases
Previous adverse event	
Injection site reaction	35
Systemic event	
Skin manifestation	69
Urticaria/angioedema	66
Fever + other mild symptoms	37
Neurologic symptoms	35
Hypotonic-hyporesponsive episode/persistent screaming	31
Organ disease ^a	18
Migraine	17
Vaccine hypersensitivity ^b	14
Vasculitis	7
Arthralgia/arthritis	6
AEFI to other vaccines	5
Thrombocytopenia	4
Others	24
Total	368
Suspected contraindication	
Personal story of	
Neurologic disease	61
Allergic disease	60
Vaccine hypersensitivity ^b	38
Autoimmune disease	34
Immunodeficiency	26
Congenital disease	15
Organ disease ^a	13
Migraine	12
Skin disease ^c	11
AEFIs to other vaccines	9
Drug allergy	7
Kawasaki syndrome	6
Others	13
Personal story of	
Previous adverse event	31
Family history of diseases ^d	16
Fear of risk of AEFI ^e	33
Total	385

^a Organ disease: hepatic, hematologic, respiratory, cardiovascular, renal, gastrointestinal disorder.

^b To the vaccine or its component (i.e. preservative, contaminant, adjuvant).

^c Including eight urticaria.

^d Severe allergic diseases, immunodeficiency, neurologic disorders.

^e Including 30 HLA "at risk" as false contraindication stated from one single private physician.

3.2. AEFI surveillance

Throughout the surveillance period (1993–2003), 3023 report sheets were evaluated and classified. Classification of data by type of vaccine administered is shown in Table 2. Although the highest AEFI frequencies were reported for diphtheria–tetanus (DT) and tetanus toxoid (TT) vaccinations, as previously observed [4], since 2001, an increasing number of AEFIs had been related to the recently introduced hexavalent (DTaP–IPV–HB–HIB) vaccine.

Table 2
Distribution of reports by vaccine administered

Vaccine	Number (%)
DT	589 (19.5)
TT	503 (16.6)
HB	389 (12.8)
DTPw	254 (8.4)
MMR	213 (7)
Hexavalent	188 (6.3)
Influenza	154 (5.1)
DTaP	107 (3.5)
Tetavalent (DTaPHB)	61 (2)
DTPw + HB + OPV	60 (2)
HIB	47 (1.5)
DTaPHB + OPV + HIB	38 (1.2)
Pneumococcal	38 (1.2)
DTaPHB + IPV	27 (0.9)
Typhoid oral	24 (0.8)
BCG	24 (0.8)
aP	22 (0.7)
Measles	21 (0.7)
DTaPHB + IPV + HIB	19 (0.6)
MMR + HB	17 (0.5)
OPV	16 (0.5)
DTaPHB + OPV + HB	14 (0.4)
DTaPHB + OPV	13 (0.4)
DTaPHB + HIB	13 (0.4)
Pentavalent + HB	10 (0.3)
IPV	10 (0.3)
Other single or combined ($n < 10$)	152 (5)
Total	3023 (100)

DT, diphtheria–tetanus vaccine; TT, tetanus vaccine; HB, hepatitis B vaccine; DTPw, diphtheria–tetanus–pertussis whole cell vaccine; MMR, measles–mumps–rubella vaccine; IPV, inactivated polio vaccine; hexavalent, DTaP–IPV–HB–HIB; DTaP, diphtheria–tetanus–acellular pertussis vaccine; tetavalent, DTaPHB; OPV, oral polio vaccine; HIB, *Haemophilus influenzae* type B vaccine; BCG, tuberculosis vaccine; aP, acellular pertussis vaccine; pentavalent, DTaP–IPV–HIB.

The age groups more frequently involved were similar to those previously reported: adolescents and adults aged >13 years (34%), and children <1 year (24%). The time of onset of symptoms also appeared in the range of that reported in previous years.

The 5386 events described in 3023 forms were ranked according to system organ classification as shown in Table 3. General disorders, local and systemic skin manifestations and neurological events had the highest frequencies.

The degree of causality was judged definite in 67.2% of reports, probable in 26.2%, possible in 3% and unrelated in 3.5%. An additional 0.1% was unclassifiable for essential data missing.

The 2917 cases judged as definite, probable or possible were subdivided into common (75%), relevant (20%), and serious (5%). All 145 serious events, reported in Table 4, were thoroughly evaluated through complete records and followed up. Only 56 of them could be classified as definite; they included severe local reactions (one-third after BCG injection), anaphylactic shock and one of the cases of thrombocytopenia. Sixty-one serious events were judged probable and 38, showing an uncertain causal correlation with vaccine administra-

Table 3
Reported events ranked by system organ classes

System organ classes	Number ^a
General disorders	1520
Application site disorders	1309
Skin and appendages disorders	680
Central and peripheral nervous system disorders	479
Gastro-intestinal disorders	384
Psychiatric disorders ^b	342
Musculo-skeletal system disorders	314
Respiratory system disorders	75
White cell disorders	56
Vascular extracardiac disorders	52
Cardiovascular disorders, general	50
Vision disorders	36
Platelet, bleeding and clotting disorders	19
Heart rate and rhythm disorders	14
Metabolic and nutritional disorders	11
Urinary system disorders	11
Liver and biliary system disorders	7
Endocrine disorders	5
Immune system disorders	5
Hearing and vestibular disorders	5
Other special senses disorders	4
Secondary terms	3
Reproductive disorders, female	2
Neonatal and infancy disorders	2
Red blood cell disorder	1
Total	5386

^a Each report might include multiple adverse events.

^b Including anorexia, somnolence, insomnia, nervousness, agitation.

Table 4
Serious AEFIs reported in the surveillance period

Event	Number
Local reaction	50
Febrile convulsion	29
Afebrile convulsion	14
Encephalopathy	8
Thrombocytopenia	5
Ataxia	5
Anaphylaxis	5
Facial paralysis	4
Vasculitis	4
Guillain Barré syndrome	3
Myopathy	2
Lymphocytic meningitis	2
Strabismus	2
Transverse myelitis	1
Serum sickness	1
S. Henoch purpura	1
Left cardiac failure	1
Respiratory insufficiency	1
Persistent vertigo	1
Hepatitis	1
Taste and smell disorder	1
Proteinuria	1
Succlavian thrombosis	1
Brachial neuritis	1
Speech disorder	1
Total	145

tion, were defined possible. They all recovered completely except for five cases, which are still presenting sequelae, and four currently under therapy. The overall average rate of AEFIs reported in the Veneto region was 2.6 per 10,000 administered doses. Rates per specific vaccine have been calculated for 2002, due to improved collection of data regarding administered vaccines: DT showed the highest dose-based rate, with 12.9, followed by the hexavalent with a 10.7 rate and TT with 5.26; MMR had a 5.1 dose-based rate.

4. Discussion

AEFIs surveillance is an essential activity in assuring a high standard of vaccine safety as required in modern immunization programs. Monitoring and accurate assessment of causality correlation, particularly in cases of serious and unusual events, is necessary to prevent loss of confidence, decreased vaccine coverage and risk of the return of epidemics of preventable diseases [7]. Advanced systems also have means to perform correct post-marketing surveillance of new vaccines, to assess signals of potential adverse events detected by passive reporting and to design ad hoc studies to clarify hypotheses [8].

To further improve immunization safety activity, some countries established worldwide-specialized centers for AEFI assessment and management at the risk of individuals. CDC's Clinical Immunization Safety Assessment (CISA) network, the United States Military's Vaccine Healthcare (VHC) Centers, Australia's Special Immunisation Services, The Netherlands Vaccination Programme Safety Surveillance System and the Green Channel described here are examples of clinical evaluation centers interfaced with surveillance systems in different countries. These centers also offer the opportunity to improve the understanding of the mechanisms and risk factors of adverse reactions. They also represent a powerful response to public concern of AEFIs, often enhanced by media and web site's incorrect information [9], and can be useful for risk and benefit communication, clarifying perceived and real risks for the individual and the community. Dealing with low rates of clinical events, collaboration between these centers to share data and experience strongly enhances the possibility to validate the findings and correctly identify previously unrecognized syndromes.

The Veneto region safety activity, born in 1992 also in response to movements, is currently operating in Italy and is now active in the evaluation of complex cases of AEFIs, and in monitoring the safety of new licensed single and combined vaccines. It also applies to the international collaboration on specific issues to satisfy the current safety demand.

The overall activity confirmed the usefulness of the Green Channel at regional level in the prevention of AEFIs and safe management of immunization in single individuals, or in identifying the need of very selected suspensions or exemptions. From the entire study population it appears that the majority of the subjects evaluated (73%) were found eli-

gible for vaccination; in particular, 68% of these were actually vaccinated under standard or protected conditions. These individuals could have been incorrectly exempted in the absence of a specialized assessment. Also LHU personnel took benefit and learned from specialized management of the subjects evaluated.

The Veneto region AEFIs surveillance system represents a useful source of data for monitoring currently used and also new vaccines, not only for local purposes but also as a reference center for specific questions raised at the national level. Although the number of reports is not high and data are biased by underreporting and excess in mild and known AEFIs reporting, the system can give information and signals on events that can be further assessed individually. For example, a small group of immediate reactions after an MMR product is now on analysis to identify the responsible component.

The collected data of the surveillance period confirmed that the most frequent AEFIs are derived from diphtheria and tetanus toxoids, with injection site reactions in more than 50% of reports, but the increasing reporting of AEFIs after the hexavalent vaccine deserves attention and further evaluation to assess its reactogenicity after the initial period of natural increased reporting due to its recent introduction.

As regards to the serious AEFIs, the great majority of the subjects affected recovered without sequelae; five persons with persistent manifestations, mild in two of them, belonged to the “possible” or “probable” category.

In conclusion, the Green Channel system contributed to vaccine safety surveillance and perception of risk/benefit in our region, providing a prompt assessment of individuals at risk of AEFI, and monitoring adverse events with back information to LHU officials. The Green Channel model could be more effective if expanded at national level and connected with international similar centers for surveillance and post-marketing evaluations.

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