doi: 10.1111/j.1365-2222.2012.03985.x
Clinical & Experimental Allergy, **42**, 1088–1096

ORIGINAL ARTICLE **Clinical Allergy**

Vaccine allergy evaluation and management at the specialized Green Channel Consultation Clinic

F. Micheletti[1], D. Peroni[2], G. Piacentini[2], V. Schweiger[3], R. Mirandola[4], E. Chiesa[5] and G. Zanoni[5]

[1]National Centre for Immunobiologicals Research and Evaluation, Istituto Superiore di Sanità, Rome, Italy, [2]Pediatric Department, University of Verona, Verona, Italy, [3]Anaesthesiology and Surgery, University of Verona, Verona, Italy, [4]Biostatistics Unit, University Hospital of Verona, Verona, Italy and [5]Green Channel Centre of the Veneto Region, Immunology Unit, University Hospital, Verona, Italy

Clinical & Experimental Allergy

Summary

Background Suspected vaccine allergy may be a cause of incomplete or delayed vaccination. Patients at risk of adverse reactions or suspected contraindications need specialized consultation about subsequent vaccinations.

Objective To analyse consultancy results for patients at risk of allergic reactions to vaccines as evaluated by the Green Channel University Hospital Immunization Consultancy Clinic.

Methods A review of cases of allergic reactions to vaccines or contraindications due to underlying diseases or sensitization to vaccine components submitted to the Green Channel was carried out. Analysed data included detailed clinical reaction history, skin and *in vitro* allergy testing with vaccine components, recommendations for vaccination and outcome of subsequent vaccine administrations.

Results A total of 519 cases, 370 referred for previous local or systemic reactions to vaccines, mostly cutaneous, and 149 sent for suspected contraindications were evaluated. Skin testing was performed on 152 patients, specific IgE determination in 37 subjects and patch testing in 173 cases. After consultation, 442 (85%) subjects were advised to continue vaccination, with personalized precautions (premedication, or alternative brand, or administration in graded doses) for 200 of them. Among the 352 (80%) patients vaccinated as per Green Channel instructions, 33 subjects (9.3%) reported mild allergic or non-specific symptoms and one (0.3%) urticaria with bronchospasm.

Conclusion and Clinical Relevance Even though vaccine allergy occurs very rarely, a safe procedure for immunization can be applied, through specialized allergy consultancy, for most subjects with suspected allergy to vaccines, and who could be potentially excluded from vaccination for risk of adverse reactions.

Keywords allergic reactions, consultancy, sensitization, vaccines

Abbreviations AEFI, adverse events following immunization; ARV, allergic reactions to vaccines; CI, confidence interval; GC, Green Channel; OR, odds ratio; PHU, Public Health Unit; aP, acellular pertussis vaccine; BCG, tuberculosis vaccine; DT, diphtheria-tetanus vaccine; DTaP, diphtheria-tetanus-acellular pertussis vaccine; DTP, diphtheria-tetanus-whole cell pertussis vaccine; HA, hepatitis A vaccine; HB, hepatitis B vaccine; Hexavalent (DTaPIPVHBHiB), diphtheria-tetanus-acellular pertussis-inactivated polio-hepatitis B-*Haemophilus influenzae* type b vaccine; Hib, *Haemophilus influenzae* type b vaccine; HPV, human papilloma virus vaccine; INF, influenza vaccine; IPV, inactivated polio vaccine; Men C, meningococcal C vaccine; MMR, measles-mumps-rubella vaccine; MMRV, measles-mumps-rubella-varicella vaccine; OPV, oral polio vaccine; PCV, pneumococcal vaccine; TBE, tick-borne encephalitis vaccine; TT, tetanus vaccine; VAR, varicella vaccine; YF, yellow fever vaccine.

Submitted 26 August 2011; revised 10 February 2012; accepted 13 February 2012

Correspondence:
Giovanna Zanoni, Green Channel Centre, Immunology Unit, Department of Pathology, University Hospital, Piazzale L.A. Scuro 10, 37134 Verona, Italy.
E-mail: giovanna.zanoni@univr.it
Cite this as: F. Micheletti, D. Peroni, G. Piacentini, V. Schweiger, R. Mirandola, E. Chiesa and G. Zanoni, *Clinical & Experimental Allergy*, 2012 (42) 1088–1096.

Introduction

Currently available vaccines are safe, but adverse events can be observed and although are usually mild, on rare occasions there can be serious reactions such as anaphylaxis [1]. To maintain public confidence in vaccines therefore advanced immunization programmes must include activities for vaccine safety monitoring at the individual level. Localized and systemic skin manifestations are common vaccine reactions [2, 3]. When allergy to vaccine components, i.e. infectious agents or other potential allergens, is suspected, vaccine allergy experts are needed to advise on subsequent administrations. Hence, in a few countries, specialized activities for pre- and post-vaccination consultancy for subjects at risk have been established [4, 5].

In the Veneto region of Italy, a University Hospital Consultancy Clinic for adverse event following immunization (AEFI) prevention and surveillance, named the 'Green Channel' (GC), has been active since 1992 [3] and has the following tasks:

Specialized pre-vaccination consultancy for Public Health Unit (PHU) personnel to evaluate vaccination eligibility for subjects with history of previous AEFI or contraindications;

Surveillance system management of AEFIs reported in the Veneto region, which includes their analysis and classification and publication of annual reports.

We carried out a review of cases submitted to the GC for consultation on suspected allergic reactions to vaccines (ARV) or contraindications due to underlying allergic diseases, which were evaluated by a clinical immunologist for subsequent vaccination management.

The primary aim of this review is to analyse the outcome of consultancy concerning safe vaccination of subjects at risk and to correlate the results with selected variables. A further long-term objective is to assess the impact of GC activity in improving vaccine personnel's knowledge regarding the need for specialized hospital consultancy.

Methods

Study population

Subjects with suspected allergy to vaccines were singled out from the 1425 cases submitted to the GC in 1992–2009 period, for vaccination eligibility consultancy. Patient data were extracted from the GC database regarding demographic data, detailed clinical history, allergy testing, recommendation for vaccination and follow-up of all submitted cases. Clinical selection criteria for allergy consultancy are based on evaluation of previous suspected ARV, including injection site reactions or systemic skin manifestations (immediate – within 1 h – urticaria, non-immediate – onset after more than 1 h – urticaria, dermatitis, discoloured leg syndrome [6], rash, erythema), respiratory symptoms, gastrointestinal, anaphylactic reactions [7], and on suspected contraindications to immunization due to sensitization to vaccine components, severe underlying allergic diseases and previous episodes of anaphylaxis.

Each of the submitted cases was evaluated by clinical and/or in-depth record examination. When indicated (Fig. 1), *in vivo*/*in vitro* allergy testing was performed, to identify specific sensitizations to vaccine components according to recommended practices [8, 9]. Finally, a conclusive report was sent to the PHU physician containing recommendations for subsequent vaccination with the standard procedure or individualized precautions, such as premedication, temporally separated single injections, alternative brand, and/or administration in hospital with full strength or graded doses [8, 9].

Patients from the province of Verona who needed vaccine administration in hospital were directly managed by the GC staff, whereas people from other areas of the Veneto region were given instructions for vaccination in their areas of residence. In cases of serious ARV or contraindications or patients with sufficient protection, temporary suspension or exemption was recommended.

Revaccination results of each patient were checked annually through contact with the referring physician to record vaccines administered and type of AEFI manifested, if any, that were divided into ARV and non-specific symptoms.

Consultation data are discussed and regularly published in GC activity annual reports for PHU personnel and regional vaccine policy-makers.

Ethics committee approval was unnecessary because this article represents a review of internal Green Channel data, which have been elaborated and managed as per Italian privacy laws (Law n. 196/2003).

Allergy testing

When necessary (Fig. 1), patients underwent vaccine skin testing in a hospital setting (prick test with full-strength vaccine, intradermal test with 1 : 100 and 1 : 10 dilution) or prick test with specific food components present in selected vaccines (egg proteins, yeast, porcine gelatin), performed and interpreted according to current guidelines [8, 9]. In cases of positivity to prick or intradermal test with toxoids or yellow fever vaccine and the need for vaccination, patients received graded doses of vaccine at 15 min interval, according to published protocols [8, 9]: 0.05 mL of 1 : 10 dilution, 0.05 mL at full strength followed by 0.1, 0.15 and 0.20 mL at full strength, through the recommended route of vaccine administration, i.e. intramuscular for

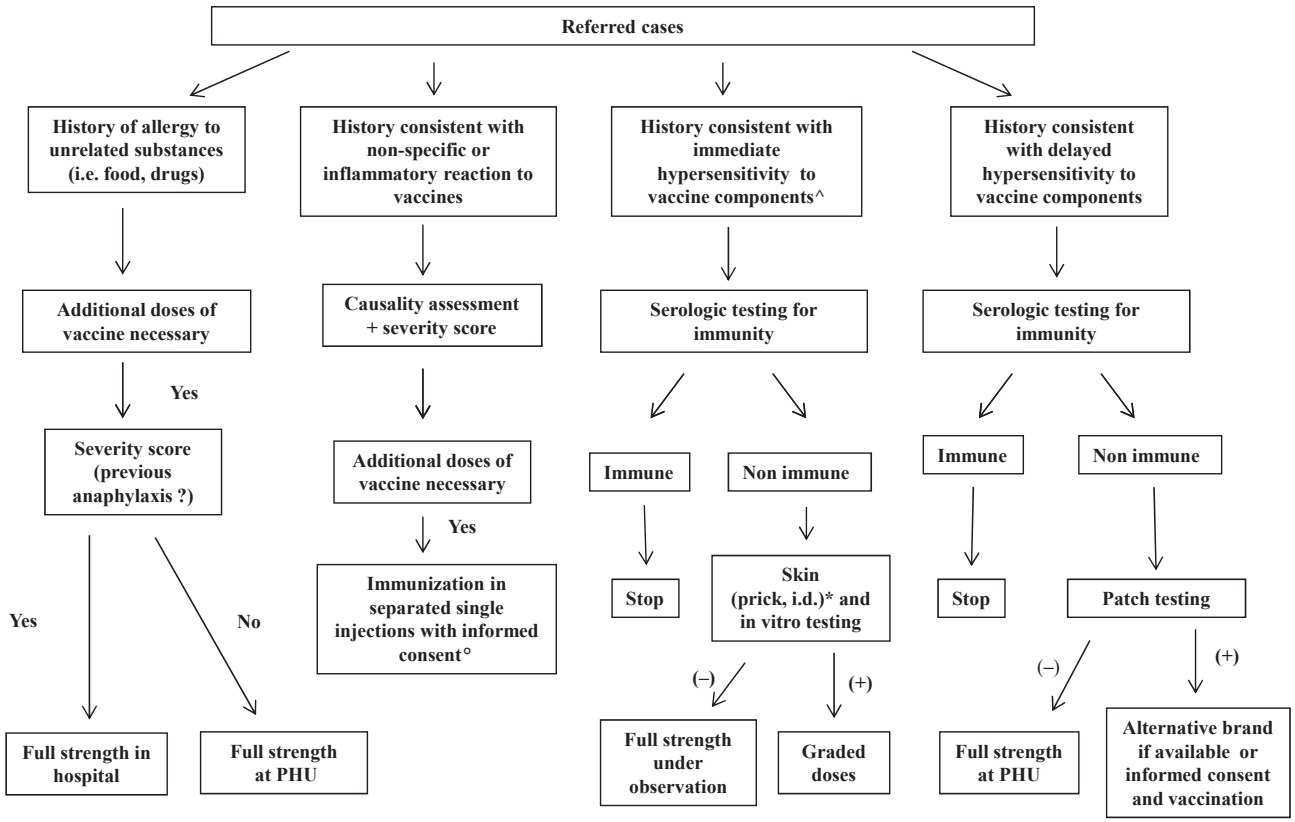

Fig. 1. Green Channel algorithm for management of suspected vaccine allergy.
°In cases of non-serious reaction; ^Egg, gelatin, immunizing agent; *Not indicated for MMR.

toxoids and subcutaneous for yellow fever. After the last dose, subjects were kept under observation for 2 h. As skin testing is not useful for MMR vaccine, children with egg allergy receive a recommendation for vaccination with full strength vaccine either at a PHU or in a hospital setting, according to the severity of the reactions to food containing egg or in the presence of active asthma [10].

In cases of delayed reactions, patch testing was performed by using Haye's Test Chamber® (Alphen aan den Rijn, the Netherlands) with a panel of 10 vaccine components present in vaccines used in Italy: antibiotics, inactivating agents, preservatives, adjuvants (5% polysorbate 80, 0.1% thimerosal, 1% formaldehyde, 10% kanamycin sulphate, 3% polymyxin B sulphate, 5% streptomycin sulphate and 25% gentamycin sulphate, (F.I.R.M.A. SpA, Florence, Italy); 1% phenoxyethanol, 10% aluminium hydroxide and 20% neomycin sulphate; Brial Allergen GmbH, Greven, Germany); the tape of patch test was removed at 48 h and readings were performed at 48 and 72 h based on ICDRG criteria [11]. Patch test results that were equivocal were considered positive. Positivity to patch test was managed as follows: if vaccination was necessary, an alternative brand of vaccine was sought where available; in other cases, the vaccine containing the positive apten was administered after written consent and after the patient was informed about the potential risk of a delayed cutaneous non-life-threatening reaction. In cases of coincidental positivity to substances not included in vaccines to be administered, the result was considered 'not relevant' for the present analysis. Specific IgE determination to available vaccine components, i.e. tetanus toxoid and food proteins was performed by ImmunoCap (Phadia, Uppsala, Sweden). Results higher than 0.35 KU/L were considered positive.

Statistical analysis

Statistical analysis focused on four outcomes: post-investigation eligibility, consultancy outcome, vaccination outcome and possible ARV (Fig. 2).

A set of independent variables were also analysed. Demographics included gender and age < 13 or ≥ 13; the cut-off of 13 years of age was chosen on the basis of the Italian vaccination schedule to include mandatory vaccinations of adolescents. To evaluate the influence of potential confounders, such as the distance from the GC immunization clinic, the Public Health Unit variable was introduced to divide the population into two groups, according to geographical distribution,

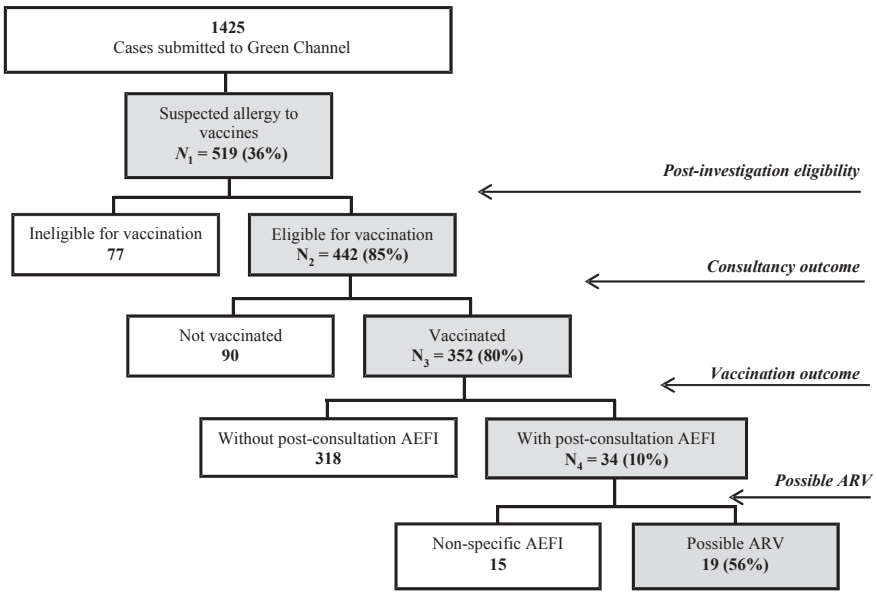

Fig. 2. Outcomes evaluated for statistical analysis of cases submitted to Green Channel (N_1, N_2, N_3, N_4 numbers of cases considered for analysis).

i.e. those coming from the Verona PHU where the centre is located, vs. other PHUs located in the other six provinces of the Veneto region. Other variables influencing vaccination acceptance were referral reason (previous ARV or contraindications); direct examination of the subject at the immunization clinic or through record examination. Finally, performance and outcome of the allergy testing variable were categorized into three groups: clinically relevant positivity to a component of the vaccine to be administered, negativity or non- relevant positivity and no allergy testing.

The association between each independent variable and the four outcome variables was assessed by Chi-square and/or Fisher's Exact tests (in case of expected frequencies < 5).

To evaluate the strength of the association, a bivariate analysis was performed by calculating unadjusted odds ratios (ORs) with their 95% confidence intervals (CI). Finally, multiple logistic regression models were estimated to adjust for possible confounding effects which produced adjusted ORs (95% CI). Effect modification was also investigated. All applied tests were bilateral at $P < 0.05$. Statistical analysis was performed by Stata 11.0^{TM} (Stata Corp LP, College Station, TX, USA).

Results

A total of 519 subjects, 234 males and 285 females, mean age 13 years, median age 7.5 years (range: 2 months–87 years, standard deviation 16 years, interquartile range 13 years) corresponding to 36% of 1425 subjects submitted to the GC were singled out for suspected vaccine allergy (Table 1), and 47% of these individuals were from the province of Verona. The remaining 906 (64%) cases were referred for neurological symptoms (29%), other immuno-mediated reactions (11%), inflammatory reactions or diseases (9%), autoimmune manifestations (8%), specific organ diseases (7%), hypotonic-hyporesponsive episodes (6%), immunodeficiencies (6%), non-allergic systemic manifestations (3%), congenital or perinatal diseases (4%), severe parental anxiety (10%) and other reasons requiring specialized advice or causality assessment (7%).

Direct clinical examination was carried out on 294 (57%) subjects, while with the rest of the group, evaluation was performed by record examination; a final written recommendation was given for all of them. A total of 370 individuals were evaluated for previous local or systemic ARV and 149 subjects were referred for contraindications or underlying diseases requiring specific precautions. Previous ARVs, most frequently cutaneous manifestations, were due to combined vaccines given in the first year of age in the majority of cases, followed by HB vaccine, which became mandatory in Italy in 1991 for children and adolescents, along with tetanus and diphtheria toxoid boosters. Assessment of potential contraindications was more frequently requested for HB vaccine during the first period of its introduction, and for viral vaccines containing food proteins, such as MMR, yellow fever, varicella and influenza (Table 1).

Skin testing (prick, intradermal) with one or more brands of vaccines or their components was performed on 152 patients, specific IgE determination on 37 subjects and patch test on 173, for a total of 251 (48%) subjects who underwent *in vivo* and/or *in vitro* allergy testing; results by referral reason are reported in Table 2. Eighty patients tested positively at least once to vaccine allergens or aptens. 153 subjects resulted

Table 1. Green Channel consultancy by patient characteristic, referral reason and vaccine involved

	Patient demographics		Vaccines involved						
Referral reasons	Age < 13	Gender (F)	1st year series*	HB	MMR and/or VAR	TT/DT/DTaP booster	YF INF	Other†	Total
Previous ARV, *N.* (%)	265 (71.6)	210 (56.8)	154 (41.6)	75 (20.3)	13 (3.5)	72 (19.5)	4 (1.1)	52 (14.1)	370
Skin manifestations‡, *N.*	107	83	73	27	3	10	1	23	137
Non-immediate urticaria§, *N.*	72	54	41	25	3	16	1	13	99
Local reaction, *N.*	40	40	15	10	1	35	2	7	70
Immediate urticaria, *N.*	26	15	16	1	3	7	0	5	32
Respiratory symptoms, *N.*	12	8	4	6	1	1	0	3	15
Angioedema¶, *N.*	7	7	5	3	0	2	0	1	11
Anaphylaxis, *N.*	1	2	0	2	2	1	0	0	5
Gastrointestinal symptoms, *N.*	–	1	0	1	0	0	0	0	1
Contraindications, *N.* (%)	103 (69.1)	75 (50.3)	8 (5.4)	52 (34.9)	43 (28.9)	5 (3.4)	29 (19.5)	12 (8.1)	149
Sensitization to components, *N.*	65	44	1	17	41	3	25	2	89
Allergic disease‖, *N.*	38	31	7	35	2	2	4	10	60
Total, *N.* (%)	368 (70.9)	285 (54.9)	162 (31.2)	127 (24.5)	56 (10.8)	77 (14.8)	33 (6.4)	64 (12.3)	519

F, Female.

*1st year series: one or more vaccines administered in children aged < 1 year (DTP, DTaP, Hexavalent, Hib, HB, IPV, OPV).

†BCG, HA, HPV, IPV booster, Men C, PCV, OPV booster, TBE, typhoid oral or different combination.

‡Skin manifestations: erythema (44), dermatitis (41), rash (27), exanthema (17), discoloured leg syndrome (8).

§Non-immediate urticaria: 1–72 h after vaccination in 85 subjects; in 14 cases, with onset after more than 72 h, manifestation was not classified as vaccine-related.

¶Angioedema: up to 1 h after vaccination (3 subjects), after 1–72 h (eight cases).

‖Allergic disease (single or associated): food allergy (25), drug allergy (22), atopic dermatitis (16), bronchial asthma (22), contact dermatitis (4).

negative to allergy testing, and 18 showed positivity to other vaccine antigens not included in the product, that formed part of a series of substances tested by patch test (16 cases) or by specific IgE determination (two subjects). A total of 268 patients did not require testing, because clinical history was sufficient to exclude vaccine allergy or there was a need for administration of vaccines with components different from the ones responsible for the adverse reaction, or because vaccination was not considered necessary.

Eligibility to start or continue vaccination was established for 442 (85%) subjects, with personalized precautions for 200 of them (45%) (Table 3). This group includes 62 individuals for whom vaccination was necessary with relevant positivity to allergy testing and positive history of serious reactions to vaccine ingredients. Eleven out of 442 individuals received recommendations for selected vaccine administration due to contraindications to other vaccines. A total of 77 subjects were deemed ineligible for vaccination, including those for whom vaccination was not necessary taking into account their age or number of previous doses received, or in absence of individual risks of contracting a disease (i.e. hepatitis B in non-exposed children who suffered from previous reactions to this vaccine) and those who did not perform further examinations or prescribed skin tests (Table 3).

The consultancy outcome showed that 80% of eligible individuals were effectively vaccinated according to GC advice, and that 90% did not manifest any adverse reactions (Table 4). In 80% of cases with previous ARV, they received one or more components of the responsible vaccine. Only 34 of 352 (10%) patients reported symptoms after vaccination: 19 subjects presented possible mild ARV in all but one case of a female child affected by severe food and respiratory allergy who developed urticaria and bronchospasm after MMR vaccination in hospital, but she recovered immediately after treatment. The remaining 15 individuals reported mild non-specific AEFIs such as fever, irritability, or injection site reactions.

Despite having been deemed eligible, non-vaccinated subjects included a total of 46 (10%) subjects who refused to continue vaccination, and a higher percentage of refusals was recorded in cases of suspected ARV that were deemed to be unrelated to vaccination when compared with vaccine-related reactions, or in subjects with false contraindications (data not shown). Moreover, immunization was deferred in 17 (3.8%) subjects or not carried out with 15 (3.4%) individuals, due to different decisions taken by vaccine personnel; four subjects were already protected by previous doses. There is no information regarding outcome of vaccine administration after consultation for eight (1.8%) subjects (Table 4).

Statistical analysis showed significant associations between the set of independent variables and the 'post-investigation eligibility' outcome: younger subjects (< 13 years), those with contraindications and those

Table 2. Allergy testing by referral reason and vaccine allergen

	Skin testing					Specific IgE				Patch test			
		Positivity					Positivity				Positivity		
Referral reasons	Total tested (*N.* pos)	Egg proteins *N.*	Porcine gelatin *N.*	TT DT *N.*	Yeast *N.*	Total tested (*N.* pos)	Egg proteins *N.*	TT *N.*	Yeast *N.*	Total tested (*N.* pos)	Thim* *N.*	Amin† *N.*	Other *N.*
Previous ARV	108 (6)	2	1	3	–	24 (7)	1	6	–	149 (38)	19	17	2
Skin manifestations	32 (1)	1	–	–	–	6 (1)	–	1	–	42 (9)	7	2	–
Non-immediate urticaria	39 (0)	–	–	–	–	2 (0)	–	–	–	50 (10)	4	6‡	–
Local reaction	13 (1)	–	–	1	–	1 (0)	–	–	–	47 (15)	6	8	1¶
Immediate urticaria	13 (2)	1	–	1	–	8 (4)	1	3	–	5 (3)	1	1§	1‖
Respiratory symptoms	4 (1)	–	–	1	–	3 (1)	–	1	–	3 (0)	–	–	–
Angioedema	4 (0)	–	–	–	–	2 (1)	–	1	–	1 (1)	1	–	–
Anaphylaxis	3 (1)	–	1	–	–	2 (0)	–	–	–	1 (0)	–	–	–
Contraindications	44 (13)	10	1	–	2	13 (9)	7	1	1	24 (11)	9	2	–
Sensitization to components	29 (13)	10	1	–	2	13 (9)	7	1	1	13 (10)	8	2	–
Allergic disease**	15 (0)	–	–	–	–	–	–	–	–	11 (1)	1	–	–
Total tested (N. positives)	152 (19)	12	2	3	2	37 (16)	8	7	1	173 (49)	28	19	2

*Thim, thimerosal;
†Amin, aminoglicosides: single or combined positivity to neomycin, kanamycin, gentamycin, polymixin B,
‡One of them also positive to aluminium hydroxide and polysorbate 80;
§also positive to polysorbate 80;
¶phenoxyethanol;
‖formaldehyde;
**Allergic disease (single or associated): food allergy (25), drug allergy (22), atopic dermatitis (16), bronchial asthma (22), contact dermatitis (4).

Table 3. Consultancy advice in cases of suspected vaccine allergy

Post-investigation eligibility	Prick testing (19) *N.* (%)	Specific IgE (16) *N.* (%)	Patch test (49) *N.* (%)	Overall positive testing (80)‡ *N.* (%)	Negative or non relevant testing (171) *N.* (%)	Not tested (268) *N.* (%)	Total (519) *N.* (%)
Eligible for vaccination	16 (84.2)	11 (68.8)	38 (77.6)	62 (77.5)	151 (88.3)	229 (85.4)	442 (85.2)
At Public Health Unit	6 (31.6)	4 (25.0)	9 (18.4)	19 (23.8)	83 (48.5)	129 (48.1)	231 (44.5)
In hospital	7 (36.8)*	5 (31.3)*	5 (10.2)	14 (17.5)	39 (22.8)	45 (16.8)	98 (18.9)
Alternative brand of vaccine	2 (10.5)	0 (0)	21 (42.9)	23 (28.8)	4 (2.3)	11 (4.1)	38 (7.3)
Anti-allergic premedication	0 (0)	0 (0)	3 (6.1)	3 (3.8)	12 (7.0)	6 (2.2)	21 (4.0)
Temporally separated single injections	1 (5.3)	1 (6.3)	0 (0)	2 (2.5)	12 (7.0)	29 (10.8)	43 (8.3)
Eligible to selected vaccines	0 (0)	1 (6.3)	0 (0)	1 (1.3)	1 (0.6)	9 (3.4)	11 (2.1)
Ineligible for vaccination	3 (15.8)	5 (31.3)	11 (22.4)	18 (22.5)	20 (11.7)	39 (14.6)	77 (14.8)
Temporary suspension	0 (0)	1 (6.3)	3 (6.1)	4 (5.0)	7 (4.1)	10 (3.7)	21 (4.0)
Exemption	2 (10.5)†	3 (18.8)†	7 (14.3)	11 (13.8)	7 (4.1)	2 (0.7)	20 (3.9)
Further exams recommended	1 (5.3)	1 (6.3)	1 (2.0)	3 (3.8)	4 (2.3)	18 (6.7)	25 (4.8)
Other advice§	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.2)	9 (3.4)	11 (2.1)

*Three cases positive both to prick testing and specific IgE.
†One case positive both to prick testing and specific IgE.
‡Four cases positive both to prick testing and specific IgE.
§Evaluation of causal relationship between vaccination and AEFI (8), vaccination not necessary (3).

who received direct clinical examination were more likely to be 'eligible for vaccination' (Table 5); no relationship with allergy testing was found.

The unadjusted ORs (95% CI) confirmed associations with age, referral reason and clinical examination, giving significant values >1 for the same variables

Table 4. Vaccination outcome in cases of suspected vaccine allergy

	Skin testing					
	Positive (62)		Negative or not tested (380)		Total (442)	
	N.	%	*N.*	%	*N.*	%
Vaccinated	48	77.4	304	80.0	352*	79.6
At Public Health Unit	33	53.2	232	61.1	265	60.0
In hospital	15†	24.2	72‡	18.9	87	19.7
Not vaccinated	14	22.6	76	20.0	90	20.4
Refusals	5§	8.1	41¶	10.8	46	10.4
To be done	4	6.5	13	3.4	17	3.8
Suspended by other	3	4.8	12	3.2	15	3.4
Protected	0	0	4	1.1	4	0.9
Lost at follow-up	2	3.2	6	1.6	8	1.8

% calculated on eligible subjects.

*Possible ARV in 19 cases (Allergy testing: nine positive, three negative, seven not tested).

†Three patients vaccinated with graded doses of diphtheria-tetanus vaccine (2) and yellow fever vaccine (1).

‡One patient vaccinated with graded doses of yellow fever vaccine.

§Vaccine refused: mandatory HB in four non-exposed subjects, and MMR (1).

¶Vaccine refused: mandatory HB in 18 non-exposed subjects, interruption of primary immunization schedule (nine children), DTP boosters (four subjects), HPV (3), MMR (1), other unnecessary vaccines in five cases, refusal of all vaccines in one completely unimmunized child.

Table 5. Association between independent variables and 'Post-investigation eligibility' ($N = 519$)

	Overall *N* (%)	Eligible subjects *N.* (%)	Chi-square *P*-value*
'Post-investigation eligibility' *(outcome variable)*			
Eligible for vaccination	442 (85.2)		
Ineligible for vaccination	77 (14.8)		
Gender			
Female	285 (54.9)	237 (83.2)	0.16
Male	234 (45.1)	205 (87.6)	
Age			
$\geq$ 13 years	151 (29.1)	112 (74.2)	**< 0.001**
< 13 years	368 (70.9)	330 (89.7)	
Geographical distribution			
Other PHUs	273 (52.6)	234 (85.7)	0.71
Verona PHU	246 (47.4)	208 (84.6)	
Referral reason			
Previous ARV	370 (71.3)	305 (82.4)	**0.006**
Contraindication	149 (28.7)	137 (92.0)	
Clinical examination			
No	225 (43.3)	183 (81.3)	**0.03**
Yes	294 (56.7)	259 (88.1)	
Allergy testing			
Yes – positive	80 (15.4)	62 (77.5)	0.08
Yes – negative or non relevant	171 (33.0)	151 (88.3)	
No	268 (51.6)	229 (85.5)	

*Fisher's exact test.

(Table 6). Moreover, adjusted ORs confirmed previous results and revealed that the 'allergy testing' variable became significant, showing a higher probability of eligibility for vaccination in subjects with a negative or non-relevant positivity and for untested cases. No effect modification was found.

The associations between the other three outcomes (consultancy outcome, vaccination outcome, possible ARV) and all the considered independent variables were not significant (Chi square or Fisher's exact test *P*-values > 0.05). The adjusted analysis did not reveal any predictive variable for these outcomes (data available from the Authors).

Table 6. Unadjusted and adjusted ORs between the independent variables and the outcome 'Post-investigation eligibility' ($N = 519$)

Independent variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Gender (reference female)		
Male	1.43 (0.85–2.45)	1.18 (0.69–2.01)
Age (reference $\geq$ 13 years)		
< 13 years	**3.02 (1.78–5.11)**	**3.95 (2.24–6.96)**
Geographical distribution (reference other PHUs)		
Verona PHU	0.91 (0.55–1.53)	0.59 (0.31–1.12)
Referral (reference previous ARV)		
Contraindication	**2.43 (1.25–5.11)**	**3.62 (1.78–7.39)**
Clinical examination (reference no)		
Yes	**1.70 (1.01–2.85)**	**5.28 (2.23–12.49)**
Allergy testing (reference positive)		
Yes – negative or non relevant	**2.19 (1.09–4.42)**	**2.64 (1.21–5.75)**
No	1.71 (0.91–3.19)	**3.51 (1.47–8.40)**

OR, odds ratio; CI, confidence interval.

Significant associations at $P < 0.05$ in bold.

Logistic regression adjusted for gender, age, geographical distribution, referral reason, clinical examination, allergy testing.

Discussion

This study reveals that more than 85% of subjects evaluated for suspected vaccine allergy were eligible for vaccination: in particular, younger subjects with a significant difference, and of a total of 80% patients vaccinated, only 18 (5%) reported mild allergic symptoms and one (0.3%) a moderate allergic reaction.

Vaccine allergy can be a cause for concern and lead to incomplete or delayed vaccination if not evaluated by specialists [8]. Immunization clinics, competent in assessing AEFIs and contraindications and managing

subsequent vaccinations, are needed to deal with potential risks at the individual level. In an ideal model, both activities for AEFI surveillance and consultancy should be part of a comprehensive system for vaccine safety control, although such consultancy centres have been created only in a few countries [3–5, 12].

With this aim, the 'Green Channel' Regional Reference Centre was created to support PHU personnel and paediatricians in increased AEFI risk case management and to improve the national AEFI passive surveillance system. The Centre also participates in continued educational initiatives to improve knowledge and capacity of vaccine personnel, including discussion of case studies regarding GC patients [13]. This training programme has improved the quality of referrals: in comparison with the first period of activity, we observed a better selection of cases, reducing the submission of well-known false contraindications to vaccination, such as MMR administration in egg allergic subjects. Moreover, simple AEFI issues have been progressively managed at the PHU level, due to growing confidence acquired by professionals who can rapidly access expert advice in case of doubts and get suggestions regarding vaccination procedure on specific cases through GC tele-consultancy, an activity that is also useful in supporting vaccine personnel and avoiding unnecessary referrals to hospital as described by other authors [14, 15].

Our data demonstrate that specialized consultancy activity on vaccine allergy is necessary to manage safe immunization for at-risk individuals, who could have been potentially excluded from vaccination. These subjects are only a minority (about 50 cases per year), within a population of 4.5 million inhabitants and 1.6 million doses of vaccines administered per year, but their evaluation represents a point of excellence in the vaccination system. Detailed clinical history, when gathered by experts, can be sufficient to evaluate eligibility to vaccination in almost half of the cases, although performance of clinical examination is associated with a higher probability of being eligible. According to the current guidelines [8, 9], allergy testing with vaccines is necessary only in selected cases, when further doses are needed in individuals who are not already protected; although in our study population, positive results are more frequently associated with ineligibility, indication for vaccination is not merely based on allergy testing, but results from a comprehensive evaluation of risks and benefits. This attitude is particularly appreciated by the referring physicians and patients and their parents. In fact, if immunization with the culprit antigen is not necessary, in the presence of an increased risk of reactions, the individual is not considered eligible. However, the majority of subjects evaluated were found eligible for vaccination, in particular, those with suspected contraindications (adjusted OR = 3.62). Most of the eligible individuals were successfully immunized with the responsible vaccine or its components, by adopting standard or specific procedures, and only one at-high-risk child presented a relevant allergic reaction after administration in hospital.

A strength of our organization is the availability of outcome information of almost all recommended vaccinations, which is annually updated and reviewed in the GC reports; this is also important feedback for health-care providers and an opportunity for the Centre to check the quality of its results. Moreover, this has become an important tool in making decisions for patient management during long-term activity and also in creating internal protocols for re-vaccination in case of previous reactions.

The number of vaccination refusals is apparently high, but the data analysis showed that it was not influenced by the performance of clinical examination, but rather by the limited need of the vaccine under evaluation in the majority of cases. Although other authors have dealt with this problem [16] of parental concerns unresolved by consultancy, a future goal of our centre is to do specific surveillance of refusal reasons.

Our experience shows that specialized consultancy is needed to manage safe vaccination at the individual level when an increased risk of ARV is present. Therefore, immunization clinics should be created in all countries or regions, to give advice to patients, vaccine policy-makers and manufacturers on specific vaccine safety issues and brand and formulation choice. Moreover, a network of these clinics would represent an additional opportunity to share data regarding special cases.

Acknowledgements

The authors thank the Regional Health Authority (Dr. Giovanna Frison and Dr. Francesca Russo) for funding, Dr. Sandro Caffi for administrative management of the Green Channel, PHU personnel and consultants, Prof. Attilio Boner from the Department of Pediatrics at Verona University Hospital and Dr. Carlo Pini, from Istituto Superiore di Sanità, Rome, for collaboration, Nicoletta Spedicato and Elisabetta Veronese for assistance in the management of vaccinations. The authors are also grateful to Dr. Giuseppina Napoletano, Dr. Ilaria Lucchi, Dr. Sara Mondino, Dr. Romina Fabbrici and Dr. Giulia Bisoffi for collaboration and to Prof. Mark J. Newman for revision of the manuscript.

Conflict of interest: The authors have no conflict of interest.

Financial support: The Green Channel activities are financed by the Veneto Region Public Health Authority.

References

1 Bohlke K, Davis RI, Marcy SM *et al*. Risk of anaphylaxis after vaccination of children and adolescent. *Pediatrics* 2003; **112**:815–20.

2 Zhou W, Pool V, Iskander JK *et al*. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)-United States, 1991–2001. *MMWR Surveill Summ* 2003; **52**:1–24.

3 Micheletti F, Moretti U, Tridente G, Zanoni G. Consultancy and surveillance of post-immunization adverse events in the Veneto region of Italy for 1992–2008. *Hum Vaccin* 2011; **7**:234–9.

4 LaRussa PS, Edwards KM, Dekker CL *et al*. Understanding the role of human variation in vaccine adverse events: the Clinical Immunization Safety Assessment network. *Pediatrics* 2011; **127**(Suppl 1):S65–73.

5 Zanoni G, Berra P, Lucchi I *et al*. Vaccine adverse event monitoring systems across the European Union countries: time for unifying efforts. *Vaccine* 2009; **27**:3376–84.

6 Kemmeren JM, Vermeer-de Bondt PE, van der Maas NA. Discolored leg syndrome after vaccination-descriptive epidemiology. *Eur J Pediatr* 2009; **168**:43–50.

7 Rüggeberg JU, Gold MS, Bayas JM *et al*. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007; **25**:5675–84.

8 Wood RA, Berger M, Dreskin SC *et al*. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. *Pediatrics* 2008; **122**:e771–7.

9 Kelso JM. Adverse reactions to vaccines for infectious diseases. In: Adkinson NF Jr, Bochner BS, Busse WW, Holgate ST, Lemanske RF Jr, Simons FER, eds. *Middleton's allergy. Principles and practice*. 7th Edn. Philadelphia: Mosby ed, 2009:1189–204.

10 Khakoo GA, Lack G. Recommendations for using MMR vaccine in children allergic to eggs. *BMJ* 2000; **320**:929–32.

11 Lindberg M, Matura M. Patch testing. In: Johansen JD, Frosch PJ, Lepoittevin JP, eds. *Contact dermatitis*. 5th Edn. Heidelberg: Springer, 2011:439–64.

12 Gold M, Goodwin H, Botham S, Burgess M, Nash M, Kempe A. Re-vaccination of 421 children with a past history of an adverse vaccine reaction in a special immunisation service. *Arch Dis Child* 2000; **83**:128–31.

13 Zanoni G, Gottin L, Boner A, Piacentini G, Peroni D, Gold M. Case discussion of an immediate serious reaction to hexavalent vaccine mistaken for anaphylaxis. *Br J Clin Pharmacol* 2010; **70**:916–7.

14 Ainsworth E, Debenham P, Carrol ED, Riordan FA. Referrals for MMR immunisation in hospital. *Arch Dis Child* 2010; **95**:639–41.

15 Baxter D, Ghebrehewet S, Falconer M. Referrals to a pediatric immunization service: findings from a practice-based audit of a UK specialist immunization clinic. *Hum Vaccin* 2010; **6**:420–4.

16 Goodyear-Smith F, Wong F, Petousis-Harris H, Wilson E, Turner N. Follow-up of MMR vaccination status in children referred to a pediatric immunization clinic on account of egg allergy. *Hum Vaccin* 2005; **1**:118–22.