

A decade of vaccinating allergic travellers: A clinical audit

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Summary Adverse reactions following vaccination are rare but may include potentially fatal anaphylaxis. This audit is a retrospective review of 38 patients with a history, or potential risk, of 'vaccine allergy' referred to an Infectious Diseases Unit for vaccination over a 10 year period. A total of 59 patient encounters were recorded, of which 89.8% were uneventful. Of the 6 adverse events, 3 patients had a local reaction, 1 patient developed urticaria and 1 patient had a vasovagal episode. Only 1 patient developed anaphylaxis secondary to vaccination, and she had no prior history of vaccine allergy. Of these patients 17 had a history suggesting the need for immunological investigation but only 7 had laboratory evidence of allergy.

The differential diagnosis of anaphylaxis includes vasovagal reactions and non-specific mediator release and immunological work-up of such events can help avoid such patients being incorrectly labelled as allergic. The vast majority of immunisations are uncomplicated and patients with a history of allergic reactions to vaccination may be vaccinated safely in a controlled setting. Unduly conservative guidelines risk withholding vaccines providing protection against dangerous pathogens but which can be safely administered.

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Introduction

Vaccination has made a major contribution to public health and in the UK, a well-established vaccination programme

under the British Vaccination Schedule has substantially reduced the risk of several infectious diseases. Additional vaccines provide substantial protection for travellers.

The UK's Department of Health 'Green Book' suggests that the majority of individuals can be immunised with no ill effects, but that in some vaccination is contraindicated or should be deferred.¹ Clear contraindications include a confirmed anaphylactic reaction to a previous dose of vaccine containing the same antigens, or a confirmed

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anaphylactic reaction to another component contained within the relevant vaccine.¹ Immunosuppression and pregnancy constitute temporary contraindications for some vaccines. In the former, live vaccines have a potential for serious infection, and in the latter there is a theoretical risk of infection of the foetus. Pre-travel vaccination for pregnant travellers has been comprehensively reviewed elsewhere.² In cases of confirmed anaphylactic egg allergy the Green Book recommendation is to obtain specialist advice.¹

Allergy is an exaggerated response by the immune system to external substances, and is an important and increasing cause of morbidity and mortality in the UK.³ Allergic reactions have been classified by the Coombs and Gel criteria.⁴ In Type 1, immediate hypersensitivity, mast cell degranulation may result in anaphylaxis and urticaria. Type 2 hypersensitivity is mediated by IgG and IgM antibodies, occurring >72 h after the insult, and can cause haemolytic anaemia or thrombocytopenia. Type 3 hypersensitivity involves deposition of excess IgG and IgM immune complexes in the tissues, which cannot be cleared by the reticulo-endothelial system and cause local inflammation such as that seen in febrile drug reactions and serum sickness. Cell mediated Type 4 reactions occur when sensitised T cells release lymphokines in response to antigen contact, which manifest with contact dermatitis and graft rejection. Finally, Type V allergic reactions are the idiopathic responses such as rashes and fixed drug reactions seen 7–14 days following the insult.

Adverse effects following vaccination include pain or redness at the site of injection, fever, malaise, myalgia or rash. Idiopathic reactions or underlying medical conditions may underlie an adverse reaction to vaccination and include severe combined immune deficiency which may result in vaccine-associated paralysis following use of live attenuated polio vaccine, and idiopathic thrombocytopenic purpura following MMR.¹ Our interest is primarily in type 1 hypersensitivity reactions. Anaphylaxis following vaccination is considered a contraindication to further doses of that vaccine but is very rare, occurring in about one per million vaccine doses.¹ In the UK there were 130 reports of anaphylaxis or anaphylactic-type reactions reported to the Medicines and Healthcare Product Regulatory Agency between 1997 and 2003, a period in which around 117 million vaccines were dispensed.¹ This rate is close to the 0.65 cases/million doses documented in a North American retrospective review of 4 Health Maintenance Organisations between 1991 and 1997, covering administration of 7,644,049 vaccine doses.⁵ A recent North American review of 10 years of anaphylaxis cases from the National Vaccine Injury Compensation Program identified 53 possible cases of 'anaphylaxis or anaphylactic shock' from a total of 1819 (non-autism) insurance claims. On further review, only 9 were categorised as anaphylaxis, 4 as possibly allergic non-anaphylactic cases.⁶ Five resulted in death, whereas the Vaccine Safety Datalink study did not identify any deaths.⁵ This may in part reflect that worse outcomes are likely to result in an insurance claim. One study has suggested that spontaneously reported suspected adverse drug reactions to 15 marketed vaccines averaged one case per 450,000 doses of vaccine sold.⁷

Anaphylaxis is a potentially fatal type 1 hypersensitivity reaction that includes cardiovascular collapse, angioedema,

pulmonary oedema, bronchospasm, urticaria and loss of consciousness.¹ Although anaphylactic reactions to almost all vaccines were well described, this is now an increasingly rare event.⁸ The risk of vaccine anaphylaxis varies between vaccines, and reactions often occur following the first dose suggesting that allergy is probably to pre-sensitised constituents of the vaccine rather than the vaccine antigen itself.^{7,8} These include egg proteins, latex, gelatin, antibiotics, thimerosal, aluminium salts or formaldehyde commonly found in travel vaccines.⁸ Those with egg allergies may be at risk from vaccines such as influenza or yellow fever grown in embryonated eggs^{8–10} and egg allergy is a contraindication to influenza or yellow fever vaccination.¹ In these situations immunisation under controlled conditions or by giving incremental doses of vaccine has been suggested.^{11,12}

The current literature suggests that immunisation is contraindicated in those with confirmed anaphylaxis to a vaccine or one of its constituents and advise seeking specialist advice.¹ However withholding a vaccine may leave a traveller unprotected against the disease targeted by the vaccine. This audit assesses the experience of an Infectious Diseases Unit in vaccinating allergic travellers.

Materials and methods

Our study is a retrospective case audit of the notes of patients referred to the Outpatient Department of the Regional Infectious Diseases Unit at the Western General Hospital, Edinburgh, with potential 'vaccine allergy' where a Day Bed area facilitates close observation. Patients felt to be at risk of anaphylaxis or dangerous allergic reaction were referred to this centre for assessment and vaccination. Our study included all patients referred with prior vaccine allergy during the period 2000–2010.

Patients were identified from a log of patients admitted to the Day Bed area and examination of patient records allowed documentation of age and sex, the allergy and the nature of their previous reaction, atopic history and if the allergy was further investigated with IgE levels or radio allergeo-sorbent testing (RAST). The type of vaccine, indication, whether an intradermal (ID) test dose was administered, the outcome, therapeutic intervention, and the duration of observation was recorded.

All patients were assessed by a senior physician for the risk/benefit of the vaccination, immunological tests were requested and the specific arrangements for observation and vaccine administration were indicated. All vaccines were administered within an outpatient day bed area with full resuscitation facilities by staff trained in Immediate and Advanced Life Support, with immediate access to a cardiac arrest team.

For the purposes of this audit we use the definitions of the European Academy of Allergy and Clinical Immunology¹³:

Anaphylaxis: A severe, life-threatening, generalised or systemic hypersensitivity reaction. Hypotension and bronchospasm do not need to be present. It may be IgE-mediated (allergen-specific IgE) or non-allergic due to non-immunological causes (previously known as anaphylactoid reactions).

Hypersensitivity: Objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects.

Allergy: A hypersensitivity reaction initiated by immunological mechanisms.

Severity was graded as per Table 1.^{14,15} For the purposes of this audit moderate and severe reactions will be grouped together under the blanket term of anaphylaxis.

Results

Patient details

A total of 38 patients were evaluated, 29 female and 9 male, referred for vaccination with allergy over the period 2000–2010. The mean age was 33 years, with a range of 11–65 years. Ten were documented as having atopic disease (asthma, eczema, hay fever). The patient demographics are shown in Table 2.

Documented allergy

A range of allergies were referred to the Infectious Diseases Unit for vaccination. The commonest reason for referral was egg allergy, seen in 12 of the 38 patients (31.57%). In 6 patients multiple allergies were recorded, including food-stuffs, previous vaccines and drugs. These are tabulated in Table 3 in descending order.

Reason for referral and nature of allergy

Of the 38 patients, 33 were referred to the clinic for the administration of vaccines indicated for travel beyond the UK (86.8%). Of the remainder, 3 wished to update vaccinations indicated in the British Vaccination Schedule (7.9%) and 2 veterinary surgeons (5.3%) required rabies vaccine as an occupational necessity.

Table 1 Grading of severity of anaphylaxis.

Grade	Symptoms
1 (<i>mild</i>): skin and subcutaneous tissue only	Urticaria, periorbital oedema, angiooedema
2 (<i>moderate</i>): features suggestive of respiratory, cardiovascular or gastrointestinal involvement	Dyspnoea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), tachycardia, abdominal pain, chest or throat tightness
3 (<i>severe</i>): hypoxia, hypotension or neurological compromise	Cyanosis, hypotension (systolic blood pressure <90 mmHg in adults), confusion, collapse, loss of consciousness, incontinence

Table 2 Clinical features of patients studied.

Number of patients	38
Patient episodes	59
Male/Female	9/29
Mean age (range)	32.61 (11–65)
Age group	
11–18 years	4
19–30 years	19
31–50 years	9
>51 years	6
Patients with atopic disease	10

All cases referred had at least one allergic event documented. Four of the patients could not recollect the symptoms of their previous allergic reaction, and of these 3 had egg allergy and required yellow fever vaccine. Four patients were referred following previous anaphylaxis, 10 following previous mild reactions (angiooedema, periorbital oedema, urticaria). Other reported reactions included feeling non-specifically unwell after a vaccination, early childhood acute reactions reported to them by a parent, or febrile reactions following vaccination. One patient was referred because allergy to neomycin had been found on patch testing raising concern about vaccines containing trace amounts of neomycin, another due to a delayed response with rash and wheeze occurring 2 days after rabies vaccination. One patient was referred with a history of peri-menstrual eyelid swelling, but no specific allergen had been identified. The variety of referred 'allergic' reactions is shown in Fig. 1.

Further investigations

Seventeen patients underwent further investigation with RAST (radio allergosorbent test) and estimation of total IgE. Total IgE may be elevated in atopic patients and we interpreted this as indicating a higher risk of an allergic reaction. RAST records the amount of IgE that reacts with specifically with known or suspected antigens. This data is included in Table 4 below and the values for interpretation of RAST results in Table 5.

RAST testing was consistent with the clinically suspected allergy in 6 cases. Even where a documented allergy was confirmed, vaccination was undertaken without

Table 3 Documented allergies.

Egg	12 patients
Tetanus vaccine	8 patients
Typhoid vaccine	5 patients
Combined DTP vaccine	3 patients
Hepatitis B vaccine	3 patients
Seafood	2 patients
Penicillin	2 patients
Peanut	2 patients
Rabies vaccine	2 patients
Latex	1 patient
Smallpox vaccine (in 1962)	1 patient
Neomycin (on patch testing)	1 patient

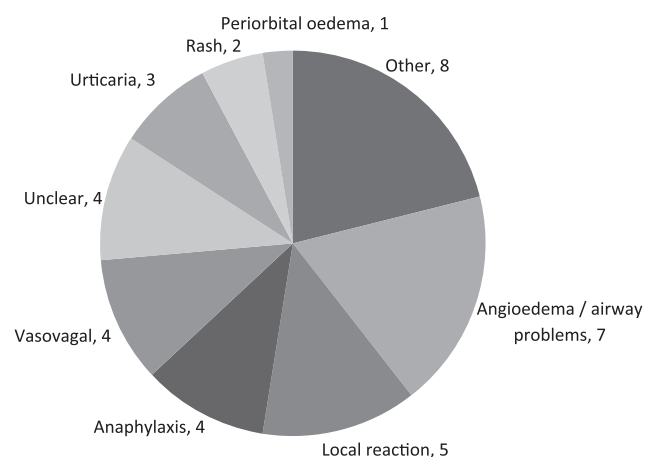


Figure 1 Nature of allergy.

complications in most cases. Two patients with RAST-proven egg allergy had a sustained flare response to ID Yellow fever vaccine. In a further 2 with RAST confirmed egg allergy, Yellow fever vaccination proceeded without incident.

Vaccines administered to patients with a history of allergy

The vaccines administered are included in Table 6. The vaccine most frequently administered was combined low dose diphtheria-tetanus-polio vaccine (TdP -Revaxis®) in 23.7% of patient episodes. Yellow fever (Stamaril®) was

Table 5 RAST interpretation.

Specific IgE level (kUA/l)	Interpretation
<0.35	No specific IgE antibody detected
0.35–0.69	Low level
0.70–3.49	Moderate level
3.50–17.49	High level
17.50–100	Very high level
100	Extremely high level

second commonest in 12 patients (20.3% of patient episodes), 9 of whom had been referred with an egg allergy. For some patients more than one vaccine was given over one or more sessions.

Management, outcome and observation period

In 26 of 59 encounters (44.1%) the history was deemed to constitute a sufficiently high probability of adverse reaction for intravenous access to be obtained prior to immunisation, and the remainder were observed in a controlled setting without IV cannulation. Of those cannulated intravenous medication was only required in one and this was expected (see below). No emergency cannulations were required in those not cannulated prior to vaccination. In one patient intradermal (ID) rabies vaccine (Rabipur®) was administered in a patient with a history of egg allergy and was given as 0.2 ml

Table 4 Allergy testing.

Documented allergy	RAST	Total IgE level (0–250 kUA/l)	Vaccine administered	Outcome
Egg, penicillin, seafood, nut	Negative	4.8	Stamaril®(yellow fever)	No complications
Egg	Negative – white	448	Stamaril®(yellow fever)	No complications
	Moderate (0.7) - yolk			
Egg	Negative	301	Stamaril®(yellow fever)	No complications
Egg	High (4.5) – egg white	67.2	Rabipur®(rabies)	No complications
Egg	Moderate (0.87) – egg white	1009	Stamaril®(yellow fever)	No complications
Egg	Moderate (1.41) – egg white	761	Stamaril®(yellow fever)	Local flare
Egg	Extreme (>100) – egg white, very high (69.1) – cows milk, mixed animal danders	587	Stamaril®(yellow fever)	Local flare to 0.1 ml ID vaccine
Egg	Negative	64.3	Stamaril®(yellow fever)	No complications
Latex	Negative – latex, mod/high – mixed danders	Not done	Revaxis®(DTP), ViATIM®(Hep A/Typhoid)	No complications
Tetanus	Negative	82.2	Revaxis®(DTP)	Urticarial rash
Hep B	Negative	4.6	Typhim Vi®(typhoid)	No complications
Rabies, shellfish	Negative	8.3	Rabipur®(rabies)	Local reaction
Rabies, Hep B	Negative	119	Twinrix®(HepA/HepB)	No complications
Multiple	Negative	44.7	Havrix Junior Monodose®(Hep A), Typhim Vi®(typhoid)	No complications
Egg, peanut	Negative – egg white	581	Stamaril®(yellow fever)	No complications
Dip/Tet	Negative	212	Revaxis®(DTP),	No complications
Typhoid	Negative	23.5	Typhim Vi®(typhoid)	No complications

Bold indicates 'positive' results.

Table 6 Vaccines administered.

Revaxis [®] (diphtheria, tetanus, inactivated polio)	14 patients
Stamaril [®] (yellow fever)	12 patients
Typhim Vi [®] (typhoid)	7 patients
Rabipur [®] (rabies)	5 patients
ViATIM [®] (hepatitis A & typhoid)	5 patients
Avaxim [®] (hepatitis A)	3 patients
Diffavax [®] (adsorbed low dose diphtheria & tetanus)	2 patients
Engerix B [®] (hepatitis B)	2 patients
Hepatyrix [™] (hepatitis A & typhoid)	2 patients
Meningitec [®] (MenC)	2 patients
Oral polio vaccine (Sabin)	2 patients
Vivotif [®] (oral typhoid)	2 patients
Epaxal [®] (hepatitis A)	1 patient
FMSE-IMMUN [®] (tick-borne encephalitis)	1 patient
Havrix Junior Monodose [™] (hepatitis A)	1 patient
Inactivated polio vaccine (Salk)	1 patient
JE-VAX [®] Biken (Japanese encephalitis)	1 patient
Twinrix [®] (hepatitis A & B)	1 patient
Verorab [®] (rabies)	1 patient

ID split between two sites. This was not a test dose but was repeated on two further occasions and subsequent rabies antibody levels confirmed a serological response. In a further 10 patients an ID test dose of vaccine at 20% of normal was administered and flare around the site of injection of 2 cm or greater present at both 30 and 60 min was taken as evidence of increased probability of an adverse reaction to vaccine administered intramuscularly (IM)/subcutaneously (SC), in which case further vaccination was not performed and follow up included serology to confirm response. Three of the 10 did not proceed to receive the remaining dose IM/SC, 1 receiving Yellow fever (Stamaril[®]), 1 purified chick embryo cell PCEC rabies vaccine (Rabipur[®]), and 1 combined polio/tetanus/diphtheria (Revaxis[®]). In all of the remaining 7 patients the ID test dose produced no untoward reaction and the remainder of the dose was administered IM/SC dependent on normal recommendations for the vaccine being administered. One patient requested a prophylactic dose of cetirizine. The observation period recommended by the physician was also individualised and ranged between 0.5 and 4 h (mean 1.87). In 7 patients the duration of observation period could not be ascertained from the notes.

One 20-year-old patient with past asthma was assessed for administration of a 3rd dose of rabies human diploid cell vaccine HDCV (Rabies Vaccine BP), having developed severe wheezing after her second dose requiring admission to our in-patient ward overnight. She did not have any history of anaphylaxis. We advised against a 3rd dose but she was travelling to a highly rabies endemic area of South Asia and was adamant that she accepted the risk of completing the course. PCEC rabies vaccine which does not contain the excipient and potential allergen phenol red was not available and after full discussion we agreed to administer the 3rd dose of rabies HDCV (Rabies Vaccine BP) under strictly controlled conditions. An intravenous cannula was inserted, and adrenaline and hydrocortisone were drawn up ready for immediate use. She developed a mild audible wheeze

within 15 min of the administration of the 3rd dose of HDCV rabies vaccine ID and 200 mg IV hydrocortisone was administered IV plus nebulised salbutamol. Her wheeze rapidly moderated, and she remained wheeze free through an extended observation period.

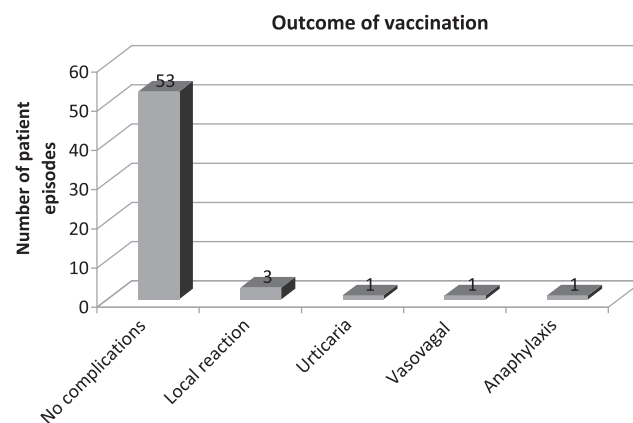
In summary 53/59 encounters were uncomplicated (89.8%). Three patients had local flare at the site of an ID test dose. One, who reported angioedema after tetanus vaccination developed an urticarial rash following TdP (Revaxis[®]) vaccination. Another who reported a local inflammatory reaction to tetanus vaccination came for observation of MenC vaccination (Meningitec[®]) and had a clearly identified vasovagal reaction. One developed wheezing as described after a 3rd dose of rabies HDCV (Rabies Vaccine BP).

Of the 12 patients receiving yellow fever vaccine (Stamaril[®]), 9 received the standard 0.5 ml SC dose, 2 had a reduced 0.1 ml ID test dose followed by 0.4 ml SC, and 1 the ID test dose alone. Outcomes are illustrated in Fig. 2.

Discussion

Adverse reactions to vaccination are recognised but rare, occurring in approximately 1% of vaccinated individuals.¹⁴ These reactions range from mild local irritation to cardiovascular collapse during anaphylaxis. This audit looked at a cohort of 'allergic' individuals referred to an Infectious Diseases Unit for vaccination over a 10 year period. In these 38 patients at potentially higher risk of vaccination-associated adverse events, 90% of vaccinations occurred without complication. Those complications that did occur were generally mild – local flares to ID test doses, urticaria and a vasovagal reaction. Only one had a mild but potentially more serious broncho-constrictive response which was managed without adverse outcome. Vaccination of this small number of patients with allergic histories was associated with safe outcomes after careful evaluation and individualised management protocols.

Our experience is similar to those of Seitz *et al.* who studied 38 individuals referred to an allergy clinic with vaccine-associated anaphylaxis.¹⁴ They underwent skin testing and challenge tests by re-vaccinating with the suspected vaccine. In all, skin prick tests were completely negative and adding this to the investigation protocol does not

**Figure 2** Outcome of vaccination.

appear to be necessary. Challenge tests with standardised doses of 10%, 30%, 60% up to 100% of the normal dose of the suspected vaccine were tolerated without side effects, suggesting that these cases were not induced by an IgE-mediated vaccine allergy. Four patients referred with a history of anaphylactic reactions had vaccination without complication.

ID doses were administered to 4 patients in our audit, and in the 2 patients receiving PCEC rabies vaccine Rabipur®, antibody titres confirmed protective immunity. One patient was given a 0.1 ml ID dose of Yellow fever vaccine (Stamaril®), and seroconversion was demonstrated at follow up review. A recent large study demonstrated that Yellow fever vaccine administered as 0.1 ml ID induces consistent protective antibody response.¹⁶

The precise nature of past reactions to vaccines is difficult to assess from history alone. Vasovagal responses may manifest with nausea, hyperventilation, paraesthesia or even convulsions and may be assumed to be anaphylactic reactions.⁸ Reactions due to non-specific release of mediators such as histamine or by indirect complement/kinin activation may also cause diagnostic confusion.^{17,18} In those with non-specific activation of the inflammatory system booster vaccinations are generally well tolerated.¹⁸ In addition contact with other allergens in the clinic environment, e.g. latex, may cause an anaphylactic reaction but the blame is attributed to the vaccine. Use of skin tests, specific IgE measurement (RAST), measurement of tryptase and drug challenge tests after a potential anaphylactic episode may help to identify true anaphylaxis and the precipitant. Such investigations may reassure patients that they are at no increased risk of adverse effects when they return for subsequent vaccination. In this audit 17 patients underwent further investigation with RAST and measurement of total IgE and 7 had abnormalities consistent with allergy.

Anaphylaxis to vaccine antigens is rare and is much more common to excipients and impurities like egg proteins and gelatin. The manufacturers of Stamaril® indicate that yellow fever vaccine is contraindicated in those with hypersensitivity to egg or chicken protein and serious hypersensitivity to a previous Yellow fever vaccination.¹ In this audit 8 of the 10 individuals with a history of egg allergy referred for yellow fever vaccination were immunised without any complication, including 2 patients with proven egg allergy on RAST testing. Two individuals with egg allergy (proven by RAST) had mild flare (<2 cms) to an ID test dose and safely received the remaining 0.4 ml of vaccine SC. Reports of uneventful administrations of egg protein-containing vaccines to those with egg hypersensitivity suggest the significance of egg allergy has been greatly over-rated.¹⁴ Individuals with gelatin hypersensitivity have been identified as at risk from the MMR vaccine^{19,20} but this audit did not identify any such patients. It has been noted that the removal of the gelatin component from vaccines in Japan has markedly reduced the incidence of vaccine-associated anaphylaxis,²¹ probably because infants are no longer sensitised to gelatin following the withdrawal of gelatin-containing DTaP.²¹

Ten of the patients in this audit had a history of atopy - hay fever, asthma, eczema. The only patient to have had what qualifies as a mild anaphylactic episode in this audit had a history of asthma, and the 2 individuals that had

a local reaction to yellow fever vaccine also both had a past medical history of eczema and/or asthma. The remaining 7 atopic patients underwent vaccination without complication. These numbers are too small to infer an increased risk of anaphylaxis in atopic individuals from this audit, but we recommend increased vigilance in atopic patients. The large study by Bohlke *et al.* of 2,226,907 children identified 5 episodes of anaphylaxis following vaccination, of which 2 were in atopic individuals.⁵

Our patients were observed after vaccination for between 0.5 and 4 h. A study of 40 anaphylactic reactions to yellow fever vaccine identified that 37.5% of reactions occurred within 30 min of vaccination, 20% within 1 h, 15% within 2 h, and 27.5% > 2 h.²² An observation period of at least 2 h will therefore allow three quarters of those who will develop an adverse reaction to do so whilst under observation.

When potentially allergic patients are referred for vaccination a detailed history of the nature of the previous reaction and the likely precipitant should be obtained. The definition of anaphylaxis is broad and it may be difficult to distinguish between true anaphylaxis, non-allergic reactions and vasovagal episodes. We suggest that such individuals should be vaccinated in a controlled setting, with appropriately trained staff, with salbutamol nebulisers and immediate access to parenteral hydrocortisone, adrenaline and chlorphenamine. In our patients only 1 patient who had intravenous cannulation needed parenteral treatment and this was expected. The addition of ID test doses may have contributed to safe outcomes in our patients. Finally, a period of observation, generally of 2 h or more following vaccination will allow reactions to be rapidly identified and treated.

In conclusion, although the risk of anaphylaxis or severe allergy to vaccines is low, the majority of patients thought to be at increased risk of adverse reaction can be safely vaccinated under tightly controlled observation. It is crucial to consider the risk-benefit balance when deciding whether to vaccinate patients labelled as allergic. To adopt overly conservative guidelines risks withholding vaccines that may protect the individual from the risk of acquiring severe, and in the case of rabies and Yellow fever, a potentially fatal infection.

Conflict of interest

We declare that we have no conflict of interest.

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