



Letter

Vaccine allergy

A decade of experience from 2 large UK allergy centers

Vaccinations prevent 2 million to 3 million deaths annually, and 1.5 million more could be avoided with better coverage.¹ Vaccinations are safe, and allergic reactions are extremely rare. In the United Kingdom, only 1 case of anaphylaxis or anaphylactoid reaction per million vaccine doses was reported between 1997 and 2003 (with no fatalities).² However, poor understanding of common and expected adverse effects often leads to misdiagnosis. No large studies using supervised single- or split-dose or multistep administration (gold standard in drug allergy workup) have been published.

Our centers receive referrals from the eastern and southern counties of England. We reviewed the clinical data of all patients with suspected vaccine allergy referred between 2007 and 2016. Ninety-five patients received 103 doses of vaccines (Table 1). This small number of referrals may have been attributable to a limited provision of allergy services in the United Kingdom, availability of Green Book recommendations and written or telephone consultations, and referral bias of predominantly adult patients to our centers.² Three-quarters of patients (75%) were 18 years or older (median age, 25 years). The referrals were instigated by primary care, occupational health physicians, or patients in 78%, 18%, and 4% of cases, respectively. Most patients (58%) experienced cutaneous reactions: nonspecific rash, urticaria, pruritus or angioedema, and presyncope or syncope. Other reactions, including fever, respiratory symptoms (dyspnea, chest tightness, wheezing), and gastrointestinal symptoms (dysphagia, vomiting, abdominal pain), were less common. Of the 20 patients with suspected egg allergy (EA), 11 were referred for influenza, 5 for yellow fever virus (YFV), 4 for measles, mumps, and rubella (MMR), and 1 for rabies vaccination. Suspected delayed hypersensitivity to neomycin led to 4 referrals. Furthermore, 9 were seen because of past reactions to an unrelated vaccine (n = 4), forgotten or unknown reasons for vaccine avoidance (n = 3), and latex allergy (n = 2).

In this large cohort of mainly adult patients, no allergic reactions occurred during vaccine administration; all patients were vaccinated successfully. There were only 3 local (localized pain, swelling, erythema) and 4 vasovagal reactions. Two patients with suspected EA referred for rabies and YFV had positive skin prick (SPT) (stock concentration) and intradermal test (1:10 dilution) results with the relevant vaccines. A 16-year-old boy had his EA disproven but had a 20-mm intradermal test wheal with Rabipur (Novartis Vaccines, Marburg, Germany). The results of tests with Rabies Vaccine BP (Sanofi Pasteur, Maidenhead, United Kingdom), which contains human albumin only, were negative, and vaccination was uneventful. This finding might suggest sensitization to a constituent of Rabipur: polygeline (colloid) or trometamol (emulsifier). An 8-year-old with confirmed EA (20-mm SPT wheal;

specific IgE [sIgE] >100 kUA/L) and a 6-mm SPT wheal with YFV was successfully vaccinated following our previously published desensitization protocol.³

Our findings indicate that vaccinations are safe and allergic reactions are vanishingly rare. Of 20 patients referred with suspected EA in more than one-third (7 of 20 patients) the diagnosis could be removed (negative SPT, sIgE test, and oral egg challenge results). The relevant vaccines were administered uneventfully. Despite clear national guidelines, 4 patients with EA were still referred for MMR vaccination.⁴ This vaccine cultured in chick embryo fibroblasts contains too small a quantity of ovalbumin to trigger an allergic reaction and is not contraindicated in EA.^{4,5} The need to refer patients for influenza vaccination remains controversial despite studies confirming that EA does not increase the risk of anaphylaxis and vaccine SPTs are not required.^{5,6} The current British Society for Allergy and Clinical Immunology guidelines still recommend SPTs before single- or split-dose influenza vaccination in patients with EA.⁴ However, most physicians adopt a more pragmatic approach of the American Academy of Paediatrics Committee on Infectious Diseases, which recommends that patients with EA can receive vaccination without additional precautions.⁷ Nevertheless, the UK Department of Health still advises that those with anaphylaxis to egg previously requiring intensive care should be referred to a specialist.⁸ The intranasal live attenuated influenza vaccine (Fluenz Tetra, AstraZeneca, Cambridge, United Kingdom) is tolerated by patients with previous anaphylaxis to egg.⁶ Our 7-step YFV desensitization protocol has been validated in adults or children with severe EA allergy.³ A generic 5-step protocol recommended by some YFV manufacturers could be used, although it has not been validated in these patient groups.

Some patients are erroneously advised to avoid all immunizations after a reaction to one vaccine only. All of them can be routinely vaccinated following standard protocols, unless an allergy to a common vaccine constituent is suspected. In latex allergy, no special precautions other than using latex-free gloves are required; only confirmed severe anaphylaxis might require vaccines supplied in vials without natural rubber.⁵ Although certain vaccines contain traces of neomycin, most antimicrobials used during vaccine production are removed during purification.⁹ Topical neomycin-related contact dermatitis is not a contraindication to neomycin-containing vaccines, and only a single case of vaccine anaphylaxis attributable to neomycin has been reported.¹⁰ In contrast, some components, such as gelatin, can lead to IgE-mediated reactions. Patients should be questioned about possible gelatin allergy and, if suspected, referred to an allergist before vaccination. Patients with previous nonallergic reactions to vaccination, such as Guillain-Barré syndrome (influenza vaccination) or encephalopathy (pertussis vaccination), should be seen by a specialist.^{2,9}

Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2017.03.010>

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Table 1
Demographics, Supervised Vaccinations, Reasons for Referral, and Outcomes

Variable	Finding (N = 95)
No. of vaccine provocation tests	103
Male:female, No.	44:51
Age, median (range), y	25 (1–75)
Reasons for referral, No. (%) ^a	
Previous reaction to same vaccine	72 (70)
Cutaneous (rash, urticaria, pruritus)	32 (31)
Angioedema	14 (14)
Presyncope or syncope	11 (11)
Respiratory (dyspnea, chest tightness, wheezing)	8 (8)
Fever	7 (7)
Gastrointestinal (dysphagia, vomiting, abdominal pain)	5 (5)
Headache	1 (1)
History of egg allergy	20 (19)
History of antibiotic allergy (delayed hypersensitivity to neomycin)	4 (4)
Other ^b	9 (9)
Vaccines suspected	
Influenza	26 (25)
Tetanus	19 (18)
Hepatitis B	14 (14)
Measles, mumps, and rubella	13 (13)
Diphtheria, tetanus, and pertussis	8 (8)
Pneumococcal	6 (6)
Yellow fever	5 (5)
Haemophilus influenzae type b and meningococcal C	3 (3)
Human papillomavirus	3 (3)
Hepatitis A and B	2 (2)
Other ^c	7 (7)
Outcomes	
No reaction	96 (93)
Vasovagal syncope	4 (4)
Local reaction (localized pain, swelling, or erythema)	3 (3)

^aOften more than one reason.^bRefer to text.^cAnthrax, BCG, hepatitis A, combined hepatitis A and typhoid, meningococcal ACWY, rabies, and typhoid.

In conclusion, routine vaccination is safe with a negligible risk of allergic reactions. Our results should reassure physicians that most (if not all) patients with suspected vaccine allergy can be vaccinated successfully. An open informed discussion about the significant benefits and a very small risk of adverse effects will assuage patients' and caregivers' fears. Although allergists are uniquely trained to investigate vaccine allergy, most immunizations could be performed in primary care (eg, MMR and influenza vaccines in EA). Unwarranted referrals generate avoidable costs and cause delays in vaccination with significant public health implications. All physicians should encourage vaccinations as far as possible. Allergists can help improve awareness and education on vaccination safety, as well as facilitate vaccinations in the few patients with confirmed allergy to vaccine and vaccine components. Reliable and regularly

updated sources, such as the UK Department of Health *Green Book* or the US Centers for Disease Control and Prevention *Pink Book*, offer advice when queries on vaccination arise.^{2,9}

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