# 8

# Vaccine safety and the management of adverse events following immunisation



## Introduction

Vaccines induce protection by eliciting active immune responses to specific antigens. There may be predictable adverse reactions (side effects): most are mild and resolve quickly. However, it is not always possible to predict individuals who might have a mild or serious reaction to a vaccine. The advice in this chapter uses the World Health Organization (WHO) classification of adverse events following immunisation (AEFIs). It gives an overview of common side effects associated with vaccines and of the management of serious adverse reactions such as anaphylaxis. The process of vaccine safety monitoring in the UK and the reporting of suspected vaccine-induced adverse drug reactions (ADRs) via the Yellow Card scheme are described in Chapter 9.

## Adverse events following immunisation

AEFIs may be true adverse reactions that are intrinsic to the vaccine, or may be caused by the way it is administered or be related to an underlying condition in the recipient. Other AEFIs may be coincidental and would have occurred regardless of vaccination.

WHO classifies AEFIs according to four main categories:

- programme-related
- vaccine-induced
- coincidental
- unknown.

## Programme-related AEFIs

These are adverse events that result from inappropriate practices in the provision of vaccination. These may include:

- wrong dose of vaccine administered
- vaccines used beyond expiry date
- vaccines used at inappropriate intervals
- inappropriate route, site or technique of administration
- vaccine reconstituted with incorrect diluent
- wrong amount of diluent used
- vaccine prepared incorrectly
- mixing into inappropriate combinations
- drugs substituted for vaccine or diluent
- vaccine or diluent contaminated
- vaccine or diluent stored incorrectly
- contraindications not elicited or ignored
- reconstituted vaccine kept beyond the recommended period.

Some AEFIs can be induced by the vaccination process itself. The administration of the vaccine causes the AEFI, rather than any of the vaccine components: for example fainting in older children and adults during the 1999–2000 meningitis C immunisation campaign (Medicines Control Agency, 2000).

## Vaccine-induced AEFIs

These are reactions in individuals specifically caused by a particular vaccine or its component parts. These may be induced, direct effects of the vaccine or one of its components, and/or due to an underlying medical condition or an idiosyncratic response in the recipient.

Direct effects of vaccines include, for example, local reactions and fever within 48 hours of DTaP/IPV/Hib, rash and fever seven to ten days after MMR, and parotitis three weeks after MMR.

An example of an AEFI due to an underlying medical condition is vaccineassociated paralysis which very rarely followed the use of live attenuated oral polio vaccine in a child with previously unrecognised severe combined immune deficiency.

Idiosyncratic responses include idiopathic thrombocytopaenic purpura (ITP) within 30 days of MMR, and anaphylaxis immediately after vaccination. When

there has been a confirmed anaphylactic reaction to a previous dose of the same vaccine, then this contraindicates further vaccinations with the same vaccine or a component of that vaccine.

This category also includes medical conditions that would have occurred at some point in an individual but are triggered earlier by the vaccination. This may include febrile seizures in a child with a family history of the same, or onset of infantile spasms (Bellman *et al*., 1983).



## Coincidental AEFIs

These are not true adverse reactions to immunisations or vaccines but are only linked because of the timing of their occurrence. When an AEFI is coincidental, the event would have occurred even if the individual had not been immunised. An example would be people who develop a cold with coryzal symptoms following flu vaccination. Flu vaccine does not prevent the common cold and colds are common in the winter when people are receiving flu vaccine.

## Unknown AEFIs

Defined as AEFIs which there is insufficient evidence to classify as one of the above.

# Common vaccine-induced AEFIs

Common vaccine-induced AEFIs include:

- pain, swelling or redness at the site of injection. These occur commonly after immunisation and should be anticipated
- local adverse reactions that generally start within a few hours of the injection and are usually mild and self-limiting. Although these are often referred to as 'hypersensitivity reactions', they are not allergic in origin, but may be either due to high titres of antibody or a direct effect of the vaccine product, e.g. endotoxin in whole-cell bacterial vaccines. The occurrence or severity of such local reactions **does not contraindicate** further doses of immunisation with the same vaccine or vaccines containing the same antigens
- systemic adverse reactions which include fever, malaise, myalgia, irritability, headache and loss of appetite. The timing of systemic reactions will vary according to the characteristics of the vaccine received, the age of the recipient and the biological response to that vaccine. For example, fever may start within a few hours of tetanus-containing vaccines, but occurs seven to ten days after measles-containing vaccine. The occurrence of such systemic reactions **does not**

**contraindicate** further doses of the same vaccine or vaccines containing the same antigens.

The types of side effect that are commonly seen after the routine and other childhood immunisations are described in the relevant chapters, along with details of when they are most likely to occur.



## Managing common vaccine-induced AEFIs

Parents should be given advice about AEFIs that they can expect and how such events should be managed. The leaflets on vaccinations provided by the Department of Health give information about AEFIs and include advice on their management.

Fevers over 37.5˚C are common in children and are usually mild. Advice on the use and appropriate dose of paracetamol or ibuprofen liquid to treat a fever should be given at the time of immunisation. Guidance on the treatment of feverish illness in children under five years of age from the National Institute for Health and Clinical Excellence can be found at - http://www.nice.org.uk/nicemedia/live/11010/30523/30523.pdf. Local reactions are usually self-limiting and do not require treatment. If they appear to cause discomfort, then paracetamol or ibuprofen can be given.

Whilst paracetamol and ibuprofen can lower the duration of fever and reduce distress, there is no evidence that they prevent febrile convulsions. It is not therefore recommended that these drugs are used routinely to prevent fever following vaccination as there is some evidence that prophylactic administration of antipyretic drugs around the time of vaccination may lower antibody responses to some vaccines (Prymula *et al.,* 2009).

**Aspirin, or medicines that contain aspirin should never be given to children under 16 years old because of the risk of developing Reye's syndrome.**

## Thiomersal

Thiomersal is a mercury based compound has been used as a preservative in the manufacture of some vaccines for many years. In the UK, none of the routine childhood vaccines contain thiomersal. Two vaccines (Anthrax and the Green Cross Japanese Encephalitis vaccine) have thiomersal added to maintain sterility of batches, and a small number of other vaccines (Engerix B®, Twinrix®, Ambirix®, Fendrix® and Fluvirin®) use thiomersal in the manufacturing

process and may therefore contain trace levels of the compound. These vaccines are identified in relevant later chapters.

Theoretical concerns have arisen around pediatric exposure to thiomersal through vaccine administration. This concern is based mainly on data following acute toxicity of a related substance, methylmercury, and from data on chronic exposure to mercury from the food chain. However, the low levels of thiomersal in vaccines have never been associated with these or similar conditions, including in children or pregnant women. Thiomersal has been linked to a very low risk of localised hypersensitivity reactions (Leventhal *et al*., 2012), which can present as redness, swelling or a rash at the injection site.

Since 1999, supported by published epidemiological evidence, several regulatory authorities and scientific committees have reviewed the safety of thiomersal in vaccines. These include the UK Committee on Safety of Medicines (CSM), the World Health Organization, the United States Institute of Medicine, and the European Medicines Agency. These reviews have consistently concluded that there is no evidence of an association between thiomersal-containing vaccines and neurodevelopmental disorders, including autism.

## Rare vaccine-induced AEFIs

Some other AEFIs occur rarely and include those that are neurological or immune-mediated. Examples include seizures, hypotonic-hyporesponsive episodes (HHE), idiopathic thrombocytopaenic purpura (ITP), acute arthropathy, allergic reactions and anaphylaxis.

### Anaphylaxis

Anaphylactic reactions to vaccines are extremely rare but have the potential to be fatal. Between 1997 and 2003, there were 130 reports to the Medicines and Healthcare products Regulatory Agency (MHRA) of anaphylaxis or anaphylactic-type reactions following immunisation (excluding the meningitis C campaign), although no deaths as a result of the reaction were reported. In that time, around 117 million doses of all vaccines were supplied to hospitals and GPs. This rate (approximately one per million vaccine doses) is similar to that reported from other countries (Bohlke *et al*., 2003; Canadian Medical Association, 2002).

Onset of anaphylaxis is rapid, typically within minutes, and its clinical course is unpredictable with variable severity and clinical features. Due to the unpredictable nature of anaphylactic reactions it is not possible to define a

particular time period over which all individuals should be observed following immunisation to ensure they do not develop anaphylaxis.

Most anaphylactic reactions occur in individuals who have no known risk factors. A single set of criteria will not identify all anaphylactic reactions. There is a range of signs and symptoms, none of which are entirely specific for an anaphylactic reaction; however, certain combinations of signs make the diagnosis of an anaphylactic reaction more likely (Brown, 2004). When recognising and treating any acutely ill patient, a rational Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach must be followed and life-threatening problems treated as they are recognised (Resuscitation Council UK, 2008).

Confusion arises because some patients have systemic allergic reactions that are less severe. For example, generalised urticaria, angioedema and rhinitis would not be described as an anaphylactic reaction because the life-threatening features – an airway problem, respiratory difficulty (breathing problem) and hypotension (circulation problem) — are not present.

Anaphylaxis is likely when all of the following three criteria are met:

- sudden onset and rapid progression of symptoms
- life-threatening airway and/or breathing and/or circulation problems
- skin and/or mucosal changes (flushing, urticaria, angioedema).

The following supports the diagnosis:

- exposure to a known allergen where the patient is already known to be allergic.

Remember:

- skin or mucosal changes alone are not a sign of an anaphylactic reaction
- skin and mucosal changes can be subtle or absent in up to 20% of reactions (some patients can have only a decrease in blood pressure, i.e. a circulation problem)
- there can also be gastrointestinal symptoms (e.g. vomiting, abdominal pain, incontinence).

Most anaphylactic reactions occur in individuals who have no known risk factors.

## Differential diagnosis

All medical and nursing staff involved in immunisation should be able to distinguish an anaphylactic reaction from fainting (syncope) and panic attacks.

**Fainting** is relatively common when vaccinating adults and adolescents, but infants and children rarely faint. Sudden loss of consciousness in young children should be presumed to be an anaphylactic reaction, particularly if a strong central pulse is absent. A strong central pulse persists during a faint or seizure.

The features listed in Table 8.1 differentiate between anaphylaxis and fainting. If the diagnosis is unclear, anaphylaxis should be presumed and appropriate management given.
There should be rapid recovery from fainting. Although symptoms of malaise may persist, the patient should recover consciousness within a few minutes.

**Panic attacks** should also be distinguished from anaphylaxis. Some individuals may suffer panic attacks even before immunisation is undertaken. Symptoms include hyperventilation that may lead to paraesthesiae (numbness and tingling) in the arms and legs. There may be an erythematous rash associated with anxiety, although hypotension, pallor or wheezing will not be present.

## Management of anaphylaxis

**Guidelines on the management of anaphylaxis have been modified to ensure agreement between the Resuscitation Council UK, the British National Formulary, the Joint Committee on Vaccination and Immunisation, and the Royal College of Paediatrics and Child Health (Resuscitation Council UK, 2008).**

All health professionals responsible for immunisation must be familiar with techniques for resuscitation of a patient with anaphylaxis to prevent disability and loss of life. A protocol for the management of anaphylaxis and an anaphylaxis pack must always be available whenever vaccines are given.

Table 8.1 Clinical features of fainting and anaphylaxis

| Onset | Fainting | Anaphylaxis |
|---|---|---|
| | Before, during or within minutes of vaccine administration | Usually within five minutes, but can occur within hours of vaccine administration |
| **Symptoms/signs** | | |
| Skin | Generalised pallor, cold clammy skin | Skin itchiness, pallor or flushing of skin, red or pale urticaria (weals) or angioedema |
| Respiratory | Normal respiration – may be shallow, but not laboured | Cough, wheeze, stridor, or signs of respiratory distress (tachypnoea, cyanosis, rib recession) |
| Cardiovascular | Bradycardia, but with strong central pulse; hypotension – usually transient and corrects in supine position | Tachycardia, with weak/absent central pulse; hypotension – sustained |
| Neurological | Sense of light-headedness; loss of consciousness – improves once supine or head down position; transient jerking of the limbs and eye-rolling which may be confused with seizure; incontinence | Sense of severe anxiety and distress; loss of consciousness – no improvement once supine or head down position |

An anaphylaxis pack normally contains two ampoules of adrenaline (epinephrine) 1:1000, four 23G needles and four graduated 1ml syringes, and Laerdal or equivalent masks suitable for children and adults. Packs should be checked regularly to ensure the contents are within their expiry dates. Chlorphenamine (chlorpheniramine) and hydrocortisone are not first-line treatments and do not need to be included in the pack.

**Immediate action**

**1 Send for additional health professional assistance (see fig 8.1 & 8.2).**
**2 Send a responsible adult to dial 999 and state that there is a case of suspected anaphylaxis.**
**3 Stay with the patient at all times.**
**4 Lie the patient down, ideally with the legs raised (unless the patient has breathing difficulties).**
**5 Administer oxygen if available.**
**6 If breathing stops, mouth to mouth/mask resuscitation should be performed.**
**7 If there is no pulse, start cardiopulmonary resuscitation.**

**All patients with clinical signs of shock, airway swelling or definite breathing difficulties should be given adrenaline (epinephrine) 1:1000 administered by intramuscular (IM) injection (never subcutaneously). For information on dosage to be given see below. The preferred site is the mid-point of the anterolateral aspect of the thigh (Simons *et al*., 1998). If there is no clinical improvement, the dose may be repeated after five minutes. Further doses of adrenaline can be given if needed.**

The use of **intravenous** (IV) adrenaline (epinephrine) is hazardous and should only be considered in extreme emergency in patients with profound shock that is immediately life-threatening. Only dilute adrenaline (at least 1:10,000) should be used, and the injection given slowly. Intravenous adrenaline should only be used by those experienced in its use and ideally with the patient being monitored (at least pulse oximetry, blood pressure, ECG).

Because of the possibility of delayed reactions, individuals who have had an anaphylactic reaction should be sent to hospital, even though they may appear to have made a full recovery.

Give high flow oxygen therapy as soon as oxygen is available. Rescuers should manage the airway according to their level of training and equipment available.

### Adrenaline (epinephrine) dosage

The appropriate dose of adrenaline (epinephrine) 1:1000 (1mg/ml) solution should be administered immediately by IM injection (see Table 8.2). If there is no clinical improvement, the dose given may be repeated after about five minutes.

**In some cases, several doses may be needed, particularly if improvement is transient.**

Table 8.2 Dose of adrenaline (epinephrine) by age

| Age | Dose of adrenaline (epinephrine) Volumes stated are 1:1000 adrenaline |
|---|---|
| Under 6 months | 150 micrograms IM (0.15ml)* |
| Over 6 months but under 6 years | 150 micrograms IM (0.15ml)* |
| 6 to 12 years | 300 micrograms IM (0.30ml) |
| Over 12 years including adults | 500 micrograms IM (0.5ml) (300 micrograms IM if patient is small or prepubertal) |

* A suitable syringe for small volumes should be used.

Auto-injectors for self-administration of adrenaline should not be used as a substitute for a proper anaphylaxis pack. However, if an adrenaline auto-injector is the only available adrenaline preparation when treating anaphylaxis, health care providers should use it.

## Cautions

Because there is large inter-individual variability in the response to adrenaline, it is important to monitor the response. Start with the recommended dose and give further doses if a greater response is needed; in other words, titrate the dose according to the effect (Resuscitation Council UK, 2008)

## Further management

Antihistamines and/or hydrocortisone are not first line drugs for the emergency management of anaphylaxis. They should be considered, however, in the further management of anaphylaxis by appropriately trained staff.

### Chlorphenamine

The appropriate dose of chlorphenamine according to age should be administered by IM injection (or by slow IV injection where appropriate) (see Table 8.3)

Table 8.3 Dosage of chlorphenamine by age

| Age | Dose of chlorphenamine* |
|---|---|
| Under 6 months | 250 micrograms/kg |
| 6 months but under 6 years | 2.5 mg |
| 6 to 12 years | 5 mg |
| Over 12 years including adults | 10 mg |

* By IM injection or slow IV injection (due to the possibility of drug-induced hypotension).



Chlorphenamine (by slow IV injection) is a useful adjunct to adrenaline in the treatment of anaphylaxis. It may be given after adrenaline and continued for 24 to 48 hours to prevent relapse.

### Hydrocortisone

The appropriate dose of hydrocortisone according to age should be administered by IM injection or slow IV injection (see Table 8.4).

Table 8.4 Dose of hydrocortisone by age

| Age | Dose of hydrocortisone* |
|---|---|
| Under 6 months | 25 mg |
| 6 months but under 6 years | 50 mg |
| 6 to 12 years | 100 mg |
| Over 12 years including adults | 200 mg |

* By slow IV or IM injection

Hydrocortisone should only be given after a severe anaphylactic attack to prevent any late symptoms.

Continuing deterioration requires further treatment, including fluid infusion. As soon as IV access is available a crystalloid solution (e.g. 0.9% sodium chloride or Hartmann's) may be safer than a colloid solution, and should be given in a rapid infusion of 1–2l, or for children 20ml/kg of body weight, with another similar dose if there is no clinical response.

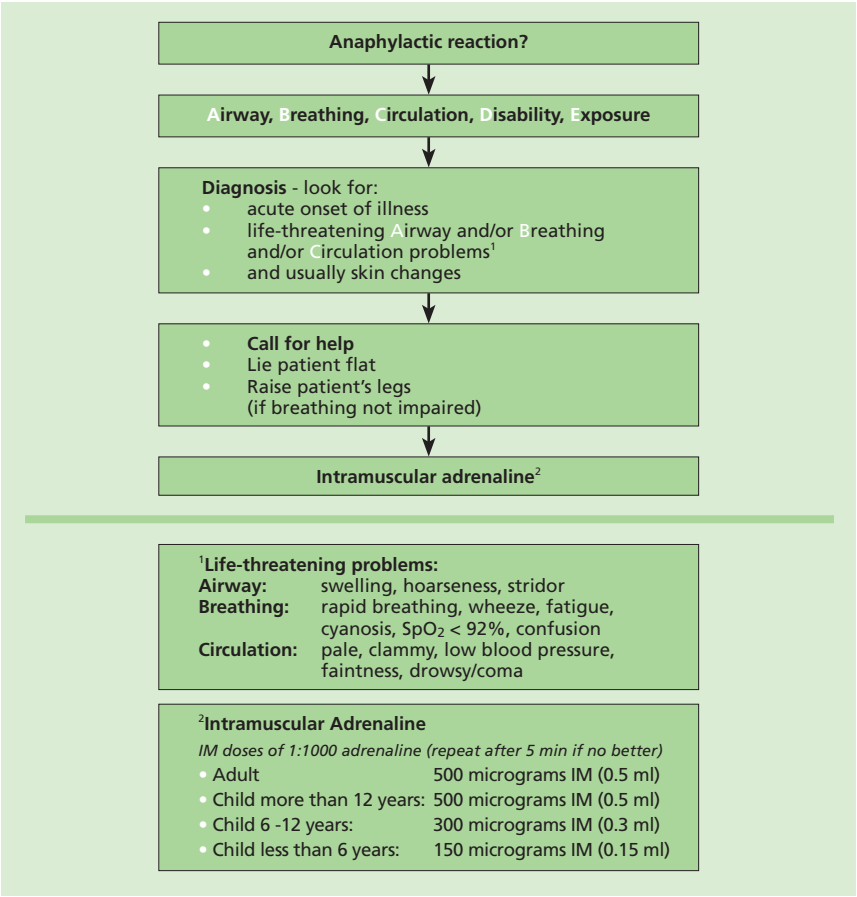


Figure 8.1 Anaphylactic reactions: initial treatment algorithm for healthcare providers (reproduced by kind permission of the Resuscitation Council UK)

An inhaled bronchodilator such as salbutamol or terbutaline is useful if bronchospasm is a major feature and does not respond rapidly to other treatment.

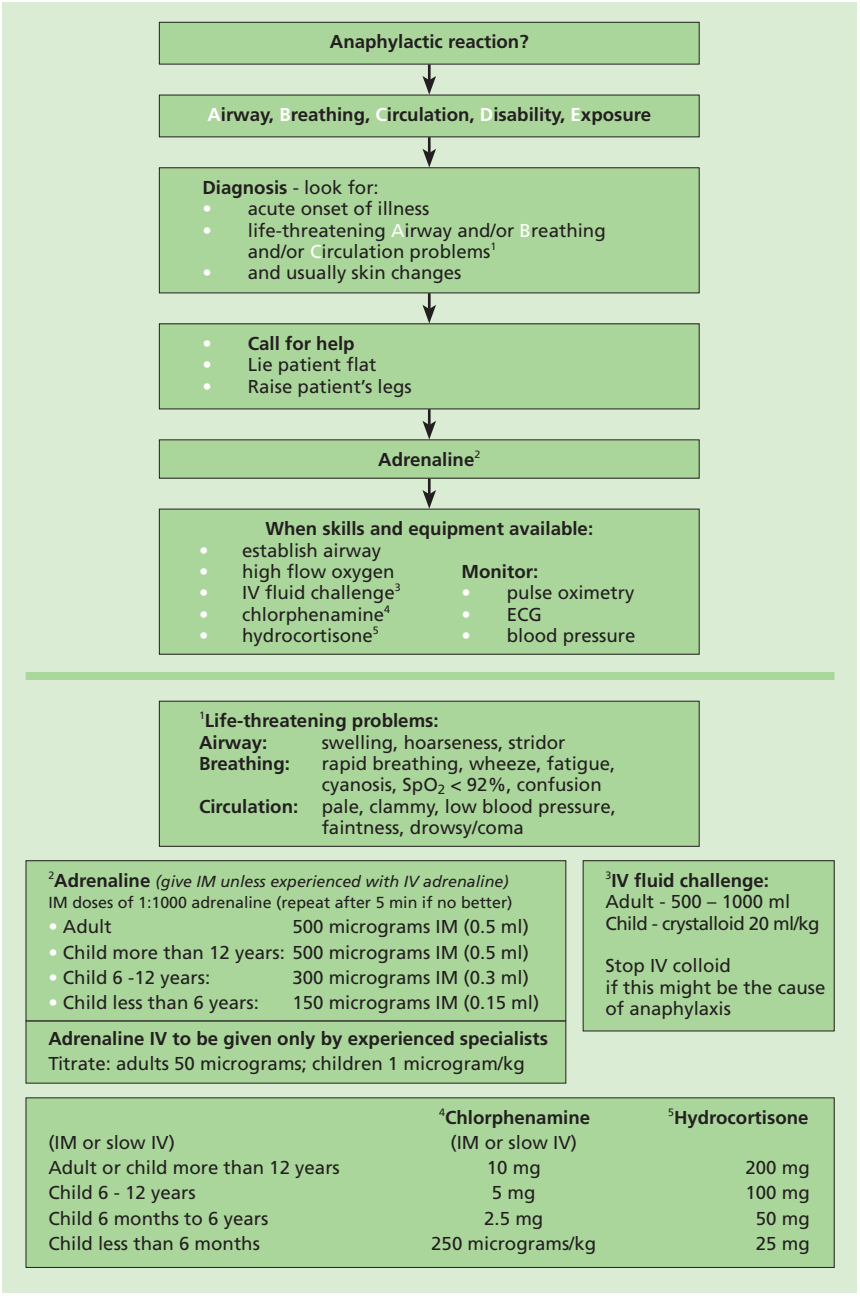


Figure 8.2 Anaphylactic reactions: full treatment algorithm for healthcare providers (reproduced by kind permission of the Resuscitation Council UK)

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