What is special about vaccine safety compared with other drugs?

Though many of the concepts relating to evaluation of drug safety are common to vaccines, there are a number of important differences that generate challenging methodological issues for those charged with vaccine safety surveillance.

First, unlike drugs that are given therapeutically to patients with disease, vaccines are given prophylactically to healthy individuals, often young children. As a consequence, expectations about vaccine safety are much higher than for therapeutic drugs. For example, a patient receiving chemotherapy for cancer will accept a high incidence of drug-induced morbidity, whereas the patient accepting a vaccine for disease prevention expects it to be ‘safe’. Although the definition of ‘safe’ is clearly subjective, in the context of vaccines, serious side effects occurring at around 1 in 10,000 are usually considered unacceptable. Detection of rare adverse events is, therefore, of paramount importance for vaccine safety surveillance.

Second, the high population exposure to vaccines, together with their administration to children around the time when unrelated developmental conditions may be naturally evolving, means that temporal associations between vaccination and serious disabling conditions will inevitably occur. When such conditions are of unknown aetiology and occur in a previously normal child, there can be a strong parental perception that a temporal association is necessarily evidence of a causal association. This is particularly so when the timing of the onset of the condition relies on parental recall, as for example in autism (Andrews et al., 2002). The ability to mount analytic studies of rare adverse events that can distinguish coincidental from causal associations is, therefore, an additional requirement for vaccine safety evaluation.

Third, vaccines have the potential to affect the unvaccinated through the indirect protection generated by herd immunity. This can profoundly change the risk–benefit balance for the prospective vaccinee. Providing that herd immunity is maintained by vaccination of the majority, then the optimum strategy for the individual is not to be vaccinated, thereby avoiding any risk from the vaccine while relying on the benefit of the protection afforded by herd immunity (Fine and Clarkson, 1986). Continued acceptance of vaccination in the face of a greatly reduced risk of disease requires an understanding of disease epidemiology and how this is affected by vaccine coverage. Ideally, it not only involves a risk assessment at the...
individual level, but also an acceptance of the concept of the public health good and the responsibility of the individual to contribute towards this. The risk–benefit for vaccines is, therefore, considerably more complicated than for therapeutic drugs, since it depends on the behaviour of the population as a whole, not just the individual.

Finally, the emergence in many countries of a vocal anti-vaccine lobby that can rapidly promote unsubstantiated claims of vaccine harm through the Internet poses a real threat to the population acceptance of vaccination. Sustaining public confidence in immunization, therefore, requires an increasingly proactive approach by those charged with managing and delivering the national vaccination programme. Unless public concerns about a vaccine’s safety can be addressed, the programme may collapse with the consequent rapid resurgence of disease, as happened with whole cell pertussis vaccination programmes in a number of countries in the 1970s (Gangarosa et al., 1998). Approaches that have been adopted to help sustain high compliance include making vaccination a requirement for eligibility for some other benefit, e.g. schooling, and ensuring that national vaccine compensation schemes are available for those who have been damaged as a result of immunization without requiring recourse to litigation. The provision of readily accessible, authoritative and evidence-based information on the risks of the disease and of the vaccine underpins these approaches.

All these factors make it essential that the systems responsible for safety surveillance are as robust as possible and are accompanied by equally robust systems for surveillance of vaccine-preventable infections.

Pathogenesis of vaccine reactions

Direct effects

As with any pharmaceutical product, adverse events from a vaccine may arise as a result of a toxic or other direct effect of one of its components. With inactivated bacterial vaccines, the inclusion of endo- or exo-toxins can result in a local inflammatory reaction at the injection site or a systemic effect such as fever. A typical example of an endotoxin-mediated adverse effect is that seen with whole pertussis vaccines (Baraff et al., 1989). Exotoxin-mediated effects are exemplified by anthrax vaccine, which consists of a cell-free filtrate of Bacillus anthracis, containing various amounts of exotoxins such as oedema and lethal factor (Brachman and Freidlander, 1999). Such toxin-mediated effects, usually occur within 24 h of immunization and resolve within a day or two. The effect of subsequent doses is difficult to predict; for example, endotoxin-mediated adverse effects are often age dependent, with an increase in reactogenicity with age. On the other hand, generation of antibody responses to vaccine toxins may result in a decrease in reactogenicity with subsequent doses.

With live vaccines, adverse events can result from the replication of the attenuated vaccine strain, the clinical picture resembling, albeit in a milder form, that seen with the wild infection. For example, attenuated measles vaccine produces a mild fever in about a quarter of children around 7–12 days after vaccination caused by the viraemia that occurs when vaccine virus replicates in the body (Peltola and Heinonen, 1986). As expected, such effects decrease with subsequent doses, as the induction of immunity prevents viral replication. On rare occasions the direct pathological effect of a live viral vaccine may be severe, as with the aseptic meningitis seen with some mumps vaccine strains; identification of vaccine virus in the cerebrospinal fluid (CSF; Forsey et al., 1992) together with
a statistically significant increased risk of aseptic meningitis in the immediate post-
vaccination period (Miller E et al., 1993) have confirmed the causal relationship with 
vaccination. Other examples of serious reactions that are directly attributable to the 
pathogenic effects of the live organisms in a vaccine are acute flaccid paralysis from oral 
poliomyelitis vaccine (OPV) and the disseminated infection seen in immunocompromised 
individuals given bacille Calmette–Guerin (BCG) vaccine.

**Immune-mediated effects**

Vaccines are designed to produce beneficial effects by the induction of immune responses to 
protective antigens in the vaccine and may also contain adjuvants such as aluminium-
containing compounds that are designed to stimulate the immune system in order to enhance 
these immune responses. Immune-mediated adverse effects are, therefore, to be expected. 
There are four main types of immune-mediated vaccine reaction (Stratton et al., 1994). 
These are as discussed below.

**Type 1 reactions: anaphylaxis and other immediate hypersensitivity reactions**

Anaphylactic reactions are rare but potentially fatal and can occur with any inhaled, ingested 
or injected pharmaceutical agent. They are caused when antigen binds to IgE antibodies on 
mast cells and basophils, causing release of mediators such as histamine. Sensitization by 
prior exposure to the antigen is required for the formation of IgE antibodies and is an 
idiosyncratic reaction. The characteristic symptoms/signs of hypotension, pallor, tachycar-
dia, subcutaneous oedema, facial swelling, laryngeal spasm and wheezing are caused by 
smooth muscle relaxation in blood vessels with constriction elsewhere. Fluid leaks from 
capillaries, causing hypotension and hypovolaemic shock. Symptoms generally occur within 
a few minutes of exposure to the allergen, although they may be delayed for a few hours 
(Stratton et al., 1994). Anaphylactic reactions can occur as a result of sensitization to 
vaccine excipients such as thiomersal (van’t Veen, 2001) and gelatine (Sakaguchi and 
Inouye, 2000; Patja et al., 2001), as well as to the intended antigenic components of the 
vaccine, e.g. diphtheria toxoid (Skov et al., 1997).

In practice, anaphylactic reactions to vaccines are extremely rare. In the UK, no fatal 
cases have been reported after any of the paediatric vaccines over the last decade, despite 
the vaccination of around a third of a million infants each year with three doses of combined 
diphtheria–tetanus–pertussis/Haemophilus influenzae type b (DTP/Hib) vaccine, and a 
similar number of toddlers and pre-school children with respectively measles–mumps– 
rubella (MMR) and a diptheria–tetanus booster. Nevertheless, all healthcare staff giving 
vaccinations are required to undergo anaphylaxis training and to have adrenaline and an 
airway to hand.

Milder forms of immediate hypersensitivity reactions, such as urticaria, facial swelling or 
wheezing but without circulatory collapse, are reported more commonly than full anaphyl-
lactic reactions. For example urticaria and facial swelling were the most common serious 
adverse events reported after a mass immunization programme with meningococcal 
serogroup AC polysaccharide vaccine in Quebec, yet even then the risk was only 9.2 per 
100 000 doses (Yergeau et al., 1996).

When any symptom/sign of immediate hypersensitivity occurs after a vaccine, then 
further doses are usually contraindicated. For combined vaccines, such as DTP/Hib, where
the antigen responsible for the hypersensitivity reaction is not known, rather than leave the child unprotected against all the diseases, vaccination in hospital with close observation may be undertaken. Use of skin tests to try and identify the responsible allergen may be unreliable and are not normally undertaken for vaccines. Desensitization to induce IgG rather than IgE antibodies has been done for some vaccines, for example tetanus (Carey and Meltzer, 1992).

**Type II reactions: interaction of antibody with normal tissue antigens**

These could theoretically occur if an antigen or other vaccine component shares a common epitope with a host tissue antigen such that the antibodies induced by the vaccine react with that tissue. Such autoantibodies may be the basis of the acute thrombocytopenic purpura reported after MMR vaccines for example (Nieminen *et al.*, 1993) but, overall, there is little hard evidence of a role of vaccine-induced autoantibodies as a cause of disease (Shoenfeld and Aron-Maor, 2000). One of the claims that MMR can cause autism is based on the postulated induction of autoantibodies to myelin basic protein (MBP) by the vaccine (Singh *et al.*, 1998), which uses embryonated chicken eggs in the manufacturing process. However, there is no evidence of MBP residues in MMR vaccines (Afzal *et al.*, 2000).

**Type III: Arthus reaction**

This is the most common cause of immune-mediated vaccine reactions and occurs when antigen combines with IgG antibody leading to deposition of antigen–antibody complexes on the walls of blood vessels and a local inflammatory reaction. Typically it is the mechanism whereby a vaccine, such as tetanus, produces increasing erythema and swelling at the injection site with each dose. As IgG antibody levels increase with subsequent doses, revaccination in the presence of excess antibody predisposes towards the formation of antigen–antibody complexes. Symptoms generally occur within a few hours of vaccination, peaking 1–2 days after. Although large local reactions often cause concern, they are self-limiting and usually resolve within a few days.

Systemic formation of antigen–antibody complexes gives rise to a generalized Arthus reaction (serum sickness) characterized by deposition in joints, skin and kidney, giving rise to arthritis, rashes and renal damage. This generalized type of type III reaction is extremely rare after vaccination, it being typically associated with administration of immunoglobulins raised in other species, e.g. the horse.

**Type IV reactions: cell-mediated/delayed-type hypersensitivity**

This occurs when antigen-specific T lymphocytes are activated by the vaccine, causing the lymphokine release and macrophage stimulation typically associated with a cell-mediated response. In a naïve individual responding for the first time to the vaccine antigen, the onset of the reaction will be delayed, peaking at about 3 weeks, whereas on revaccination the onset is more rapid, within 48 h. The classic example of a delayed-type hypersensitivity reaction to a vaccine is that seen with BCG. This is a live bacterial vaccine that replicates at the site of injection causing an ulcer that takes some weeks to heal, leaving a scar. The use of the term hypersensitivity is perhaps misleading in this context, as the BCG reaction represents a normal cell-mediated response to a replicating pathogen. However, serious adverse events
may be caused by this mechanism if a cell mediated response is induced by a vaccine antigen that cross-reacts with a tissue antigen. The occurrence of demyelination after early rabies vaccines that were produced in animal brains and contaminated with nervous tissue was likely to be due to this type of immune-mediated effect. Guillain–Barré syndrome (GBS), after influenza vaccine, may also represent a delayed-type hypersensitivity reaction although the nature of the putative cross-reacting antigens is not known.

Criteria for establishing causality for vaccine adverse events

The main planks of evidence that have been used for establishing causal associations for adverse vaccine events are summarized in Table 14.1. Although there are well-established criteria for causality assessment of adverse events for pharmaceutical products, some of these cannot be applied to vaccines. For example, unlike therapeutic drugs, vaccines offer little opportunity to study dose response, since the quantity of antigen and excipients in the product is fixed. In addition, absence of a response to rechallenge does not preclude a causal association, because of the development of immunity to the vaccine antigens. Furthermore, the application of precautionary recommendations that contraindicate further doses after a suspected serious adverse event has occurred limits the opportunity for observing the effect of rechallenge. As discussed in Chapter 7, dose response and rechallenge form one of the planks of evidence for establishing causality for drug adverse events.

<table>
<thead>
<tr>
<th>Table 14.1</th>
<th>Main criteria for establishing causality for a vaccine adverse event</th>
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<tr>
<td>Is it biologically plausible? – e.g.</td>
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<tr>
<td>• Fever after an endotoxin containing vaccine</td>
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<tr>
<td>• Acute flaccid paralysis after oral polio vaccine</td>
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<tr>
<td>Is there laboratory evidence of vaccine involvement? – e.g.</td>
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<tr>
<td>• Urabe mumps vaccine in CSF of a patient with meningitis symptoms</td>
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<tr>
<td>• Disseminated BCG in an immunocompromised patient</td>
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<tr>
<td>Is there evidence of an increased risk after vaccination? – e.g.</td>
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<tr>
<td>• Clustering in a post vaccination period</td>
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<tr>
<td>• Higher risk in vaccinated compared to unvaccinated</td>
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<tr>
<td>Is the evidence consistent across studies? – e.g.</td>
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<tr>
<td>• Consistent increased risk of aseptic meningitis within 15–35 days of a Urabe mumps vaccine</td>
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<tr>
<td>• Consistent inability to find evidence of an association between MMR vaccination and incidence or timing of onset of autism</td>
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However, other criteria, such as biological plausibility and laboratory evidence of vaccine involvement, may assume greater importance for vaccines than for non-biological agents. For example, it is biologically plausible that a live attenuated vaccine could produce reactions similar to those seen with infection due to the wild organism, although at a much lower rate. A typical example is the occurrence of acute flaccid paralysis within a few weeks of OPV. Although this could be due to unrelated conditions, such as GBS, a causal association with OPV is considered probable if the clinical syndrome is typical of poliomyelitis, the temporal relationship with vaccination is compatible with vaccine-associated paralytic poliomyelitis and alternative aetiologies have been excluded. Isolation
from the case of vaccine viruses that have mutated towards virulence provides powerful laboratory confirmatory evidence.

The ability to obtain laboratory evidence to support a causal association between a vaccine and an adverse event has, so far, been restricted to live vaccines where either the vaccine strain can be shown to be involved in the pathogenic process, e.g. BCG in the lesions of patients with disseminated mycobacterial infection (Grange, 1998) or, in the case of OPV, the excretion by the vaccinee of a mutated vaccine strain. By itself, evidence of recent seroconversion to the vaccine does not confirm a causal association, since this will be present in any recently vaccinated individual. For example, the detection of mumps-specific IgM in a child with aseptic meningitis following Urabe mumps-containing MMR vaccine cannot be used to establish a causal association since it merely confirms that the child has recently been vaccinated. Laboratory evidence supportive of a causal association would be demonstration of mumps vaccine virus in the CSF (a normally sterile fluid) with a cellular reaction characteristic of a viral meningitis (a lymphocytic CSF; Forsey et al., 1992).

If laboratory evidence is used to support a causal relationship with vaccination then it must be technically robust. Unfortunately, because of the intense media interest in vaccine scare stories, unpublished reports using unvalidated laboratory methods may be given prominence that the quality of the science does not merit. For example, a recent conference abstract reporting that measles vaccine virus had been found in gut biopsies of autistic children was given wide media publicity in the UK although it was based on an assay that could readily be shown to be incapable of distinguishing wild from vaccine virus (http://www.hpa.org.uk/infections/topics_az/vaccination/response.htm).

Even when vaccine virus or other vaccine material has been shown to be present in a lesion it does not necessarily imply a causal relationship with a clinical condition. For example, it has been shown that inactivated vaccines containing the adjuvant aluminium hydroxide can produce a local histological condition called macrophagic myofasciitis (MMF) in which macrophages containing aluminium are identified at the injection site. The detection of MMF lesions in patients undergoing muscle biopsies for myopathic symptoms has led to the suggestion that MMF causes systemic disease (Gherardi et al., 2001). However, while MMF lesions are probably a consequence of vaccination, they may nevertheless be a chance histological finding in vaccinated patients who have a muscle biopsy for unrelated symptoms and could perhaps be found with equal frequency in asymptomatic vaccinated individuals were they to have muscle biopsies performed. If this is the case, then MMF lesions are simply a ‘vaccine tattoo’ and of no clinical consequence. Indeed, the demonstration in animals of MMF-type lesions without systemic effects following injection of vaccines containing aluminium hydroxide suggests that this is probably the case (WHO, 2002).

Finally, even when there is convincing laboratory evidence of presence of a vaccine constituent in individuals with a putative vaccine reaction but not in normal controls it may simply be the consequence rather than the cause of the disease process. In the case of wild measles infection, for example, the raised IgG titres to measles and the traces of measles virus genome reported in patients with chronic active hepatitis are not thought to be the cause of the disease but rather a consequence of the underlying immunological abnormality that is the origin of the condition (Triger et al., 1972; Black, 1988). The involvement of measles virus is, therefore, a bystander effect or epi-phenomenon.

If laboratory evidence of vaccine involvement is to be used to establish a causal association between a disease and vaccination then it is important that Koch-type postulates,
employed in microbiology to establish a causal association between the presence of a pathogen and a disease, are applied to such evidence. Koch’s first postulate (evidence of the presence of the organism in cases but not in healthy individuals) is not by itself sufficient and requires additional criteria for establishing a pathogenic role for the organism, e.g. the ability to culture the organism from the diseased individual and the ability to transmit the infection by inoculation of the cultured organism. In the case of adverse vaccine events, the first of these additional criteria has been met for BCG-associated disseminated mycobacterial infection, OPV-associated acute flaccid paralysis and Urabe-associated aseptic meningitis, where replicating vaccine organisms, associated with a clinico-pathological response characteristic of the wild infection, have been shown. In the case of OPV-associated acute flaccid paralysis the second additional criterion has also been satisfied, since transmission of vaccine virus to contacts can result in the same condition. In contrast, the reported detection of fragments of measles virus genome in the intestinal tract of autistic patients with ileal lymphoid nodular hyperplasia more frequently than in children without this condition (Uhlmann et al., 2002) does not establish a causal role of measles virus in autism, since its presence, if confirmed, may simply be a consequence of a local inflammatory response in the gut of autistic children with bowel problems (Morris and Aldulaimi, 2002), as with the fragments of measles virus genome found in chronic active hepatitis (Black, 1988).

In practice, the opportunity to use laboratory evidence to support a causal association with vaccination is limited, and arguments based on biological plausibility, while supportive, are neither necessary nor sufficient. The main plank of evidence that been used to establish, or refute, a causal association between a vaccine and a subsequent clinical condition is epidemiological. The gold standard epidemiological method is the randomized controlled trial (RCT), which allows an unbiased comparison of the frequency of adverse events in vaccinated and unvaccinated groups. One classic vaccine example is the double-blind placebo-controlled crossover study in 686 twins that was specifically designed to document the true attributable risk of common symptoms after MMR vaccine (Peltola and Heinonen, 1986). This study established that the majority of the symptoms reported in the 3 weeks after MMR are not vaccine related and that the vaccine may even have a mild protective effect against respiratory infections in the post-vaccination period. However, a much larger study would be required to assess the attributable risk of more rare adverse events, such as febrile convulsions. Even when a vaccine RCT is powered for establishing efficacy it may still be of insufficient size to evaluate the risk of rare adverse events. Alternative methods that can be used post-licensure have, therefore, been devised to assess whether the risk of a particular clinical condition is greater in the unvaccinated than the vaccinated individual, or in a particular post-vaccination risk period. These methods will be discussed in the following sections. Though such methods may lack the rigour of an RCT, converging and consistent epidemiological evidence from different studies can provide powerful confirmatory evidence of causality, or lack of it.

Pre-licensure evaluation of vaccine safety

The main safety objective during the pre-licensure vaccine evaluation phase is to document the nature and frequency of the more common side effects and to ensure that any serious or unusual adverse events in the trial cohort are detected. This involves the active follow up of
every vaccinee, at least for the occurrence of serious events. These are defined as any event resulting in death, life-threatening illness, hospitalization or permanent sequelae (see Chapter 1) even where a causal association with vaccination can reasonably be excluded, e.g. an accident. Inevitably, however the size of pre-licensure vaccine trials limits the ability to detect rare vaccine adverse events or, if they are detected, to have a statistically robust comparison of the incidence in vaccinated and placebo groups. This was situation in the efficacy trials of the live attenuated rotavirus vaccine in which intussusception occurred in 5 in 10,054 vaccinees compared with 1 in 4,633 in the placebo group. Although this difference was not statistically significant, enhanced post-licensure surveillance was established which showed that this pre-licensure ‘signal’ was indeed evidence of a true causal association (Murphy et al., 2001). Similarly, occurrence of one case of aseptic meningitis in a pre-licensure study of 10,000 children given a Urabe-containing MMR vaccine in the UK (Miller et al., 1989) prompted enhanced post-licensure surveillance. This confirmed that the true risk was around 1 in 10,000 doses and not of the order of 1 in 100,000 as previously thought (Miller E et al., 1993).

When differences in rare adverse events are found between vaccinated and placebo groups in an RCT, further studies will usually be required before licensure. This was the case in an efficacy study of acellular pertussis vaccines in Sweden, where an excess of invasive bacterial infection was seen in the vaccinated group (Storsaeter et al., 1988). Although subsequently shown to be due to chance (Griffin et al., 1992), the concern raised by this finding contributed to the delay in licensure of these vaccines. In order to maximize power for measuring vaccine efficacy the Swedish trial had been designed with a smaller placebo than vaccinated group, which unfortunately reduced power for comparing adverse events.

Other factors that can limit the ability to detect serious adverse events at the pre-licensure stage are the application of stringent exclusion criteria to potential recruits that may militate against the detection of idiosyncratic vaccine–host interactions. Interactions between vaccines, or between vaccines and other drugs, may also not come to light in pre-licensure trials, where receipt of pharmaceutical products shortly before or after the study vaccine usually constitutes an exclusion criterion. For example, administration of intramuscular injections such as antibiotics shortly after OPV has been shown to increase the risk of vaccine-associated paralysis (Strebel, et al., 1995).

In light of the increasing profile given to vaccine safety issues, and the importance of sustaining public confidence in immunization programmes, it is likely that some additional requirements will be made at the pre-licensure stage of vaccine evaluation. For example, to address frequently expressed concerns about late vaccine effects, there is now a move towards extending the period of follow-up in vaccine trials to at least 6 months after the last dose. In practice, the follow up period in an efficacy trial is usually much longer in order to allow sufficient cases to accrue in the study cohorts to demonstrate protection. However, when new vaccines are licensed without efficacy trials, as for example with combination products, extension of the usual 4–6 week follow-up period to assess immunogenicity and immediate reactogenicity would seem reasonable. Furthermore, in the wake of the rotavirus and intussusception experience, it is likely that the Food and Drug Administration (FDA) in the US will require a much larger safety database to underpin a license application for a new rotavirus vaccine, and possibly other new vaccines, in the future (Black, 2001). However, a balance needs to be struck between the amount of vaccine safety data that is required for licensure and the reliance that is put on post-licensure safety evaluation in order not to prohibit the development and evaluation of new vaccines. Comprehensive guidelines on the
pre-licensure evaluation of new vaccines have recently been drawn up by the World Health Organization (WHO, in press) to help ensure that appropriate but reasonable requirements for evaluation of vaccine safety and efficacy are put in place by national regulatory agencies (NRAs), particularly those in developing countries where new NRAs are being established.

Objectives of an ideal post-licensure vaccine safety surveillance system

Ideally, a post-licensure vaccine safety surveillance system should be able to detect novel or rare adverse events not identified at the pre-licensure stage, to measure both the absolute and attributable risks of such events and to identify risk factors so that sound evidence-based contraindications to vaccination can be developed. When signals of a putative causal association have come from pre-licensure studies or there are other grounds for focusing on certain adverse events, such as intussusception with a new rotavirus vaccine or aseptic meningitis with a new mumps vaccine, then there should be an ability to establish post-licensure surveillance of these events and to mount analytic epidemiological studies to address causality.

Although these ideal objectives may appear somewhat challenging, there are now many examples where they have been achieved. Moreover, there is an increasing use of sophisticated technical and statistical tools that have been specifically developed for the post-licensure investigation of vaccine safety.

Passive post-licensure surveillance systems

Most NRAs have established pharmacovigilance systems that include vaccines. However, because vaccines can be considered a special case, as outlined earlier in this chapter, institutions with relevant epidemiological expertise may also be involved in running the passive vaccine reporting system. For example, in the USA, the Vaccine Adverse Event Reporting System (VAERS) is run jointly by the Center for Disease Control in Atlanta and the FDA. In the UK, the Medicines Control Agency, collects and analyses vaccine adverse event reports as part of its general pharmacovigilance reporting system (the so-called ‘Yellow Card’ scheme) but will approach the Immunization Division of the Communicable Disease Surveillance Centre, or other institutions with relevant expertise, if analytic epidemiological studies of specific vaccines are indicated.

To assist countries with less well-developed pharmacovigilance systems the WHO has produced a field guide on how to establish an adverse vaccine event reporting system (WHO, 1999). As a minimum such a system should be able to detect temporal or spatial clusters of novel or serious adverse events and to investigate their aetiology, e.g. whether this is due to a problem with a particular batch or manufacturer’s vaccine, or whether there has been a programmatic error such as wrong product given or wrong route of administration. Some recent examples of the ability of routine passive surveillance systems to detect such clusters are cases of an unusual oculo-respiratory syndrome occurring within a few hours of giving a new influenza vaccine in Canada (Boulianne et al., 2001), the increased reactogenicity that occurred when a manufacturer of a tick-borne encephalitis vaccine in Austria changed production methods to remove albumen (Marth and Kleinhappl, 2001) and a cluster of infant deaths in the Yemen caused by injection of insulin instead of DTP vaccine.
In each case, an epidemiological investigation of the cluster identified the causal factor.

In addition to identifying programmatic errors or problems with particular batches or makes of vaccine, passive reports should be able to identify subgroups who may have an increased likelihood of an adverse outcome by showing an overrepresentation of individuals with a particular risk factor compared with the general population. In practice there have been few examples of this: the identification of asymptomatic vertically transmitted HIV infection as a risk factor for disseminated BCG is one example (Scheifele et al., 1998) and the demonstration that a personal history of convulsion is risk factor for a DTP-associated convulsion is another (Rosenthal and Chen, 1995).

Despite such successes, simple passive reporting systems have obvious limitations. First, reporting is inevitably incomplete even if there is a mandatory requirement to report suspected reactions, as in the USA with the National Childhood Vaccine Injury Act of, 1986. To try and improve the quality and completeness of adverse vaccine event reporting in the USA, the VAERS system was established in 1990. Under this system, reports are accepted from parents as well as healthcare professionals, a special form is provided that solicits descriptive information on the event and its treatment and outcome, a 24 h toll-free telephone line is provided and there is a list of conditions that are mandated for reporting. All fatal adverse events and other selected serious events are followed up. Information on the VAERS system is made widely available to parents, and healthcare professionals are regularly reminded to report (Rosenthal and Chen, 1995). Even with these attempts to stimulate passive reporting to VAERS, the reporting efficiency for known adverse events is still poor. For example, it has been estimated that only one in three convulsions after MMR vaccine are reported and about 1 in 25 episodes of ITP (Rosenthal and Chen, 1995). Surprisingly, the sensitivity of the UK Yellow Card system for MMR-associated idiopathic thrombocytopenic purpura episodes appears to be higher with about one in five reported (Farrington et al., 1995).

A second limitation of a passive adverse event reporting system is the inability to use the data for testing causal associations, its value being largely limited to hypothesis generation. Analysis of the distribution of onsets after vaccination to identify periods in which there may be an excess of reports can be useful in defining a priori risk periods for subsequent analytic studies, as for example with aseptic meningitis after MMR vaccines (Miller E et al., 1993). Finding an excess of passive reports in a particular post-vaccination period may suggest a causal association but could simply reflect reporter bias, based on expectations of when a vaccine-attributable effect should occur. For example, an analysis of claims submitted to the National Vaccine Injury Compensation Board in the USA involving acute encephalopathy after measles-containing vaccines found a statistically significant excess of cases with onset 8 or 9 days after vaccination. This clustering was used to argue for a causal association (Weibel et al., 1998); but, given the well-known temporal sequence between measles vaccination and onset of side effects, such as febrile convulsions associated with the vaccine-induced viraemia, preferential reporting of cases with onset in the known risk period is likely. The authors also argued biological plausibility in support of a causal association, quoting as a model the post-infectious encephalitis that occurs in about 1 in 1000 acute measles cases about a week after onset of rash. However, this is not associated with the viraemic phase of the illness, but is thought to involve a later auto-immune demyelination process. Based on the wild model, if there was post-vaccination encephalitis then this should not occur at 8–9 days but about a week after the rash, which in vaccine
recipients typically occurs 10–12 days after immunization (Miller et al., 1989). While absence of a biological explanation for an adverse event does not preclude a casual association, independent confirmation by a controlled epidemiological investigation is required to show convincingly that there is an increased risk of encephalopathy 8–9 days after a measles-containing vaccine. The only controlled study of acute encephalopathy after measles vaccine failed to find an excess after removal of cases of febrile convulsions (Miller et al., 1997).

**Active surveillance of adverse vaccine events**

Because of incomplete and potentially biased reporting with passive surveillance systems, various attempts have been made to overcome these deficiencies by establishing active systems for ascertaining adverse events after vaccination. If the active surveillance system has near-complete ascertainment of adverse events then reliable estimates of absolute risk can be derived. However, without information on the risk of such events in unvaccinated age-matched groups, causality assessment can be difficult and no estimates of attributable risk can be made.

One such active surveillance system was established in the UK to monitor the propensity of different measles vaccines to produce reactions, in particular febrile convulsions (Miller, 1982). Active ascertainment was established by ensuring that in a sentinel district all measles vaccinees were followed up by a study nurse who completed a simple questionnaire documenting significant medical events in the 3 weeks after vaccination. This surveillance was largely directed at comparison of the rates of known reactions with different vaccine strains rather than the detection of novel adverse events. Between 1970 and 1980, symptoms were documented in over 10,000 children after 62 different batches of vaccine randomly selected by the National Institute for Biological Standards and Control. No evidence of a batch or strain effect was found, and the febrile convulsion rate of 1 per 1000 in the 6–11 day post-vaccination period found in the MRC Measles Vaccine trials prior to licensure (Measles Vaccination Committee, 1966) was confirmed under conditions of routine use.

An alternative approach to active adverse event surveillance was established in Canada in 1992 with the objective of identifying all serious vaccine events that resulted in hospital admission. Specially trained nurses were installed at 11 sentinel paediatric centres with the task of reviewing the hospital notes of children admitted with possible vaccine reactions (Anon., 1993). Admissions for vaccine-preventable infections were also identified in order to provide risk assessments for the disease as well as the vaccine. The Canadian Immunization Monitoring Programme Active (IMPACT) system is labour intensive but provides a reliable measure of the absolute risk of defined adverse events of sufficient severity to warrant hospital admission and allows this risk to be compared with the morbidity attributable to the disease. However, assessment of causality is difficult and requires a judgement to be made on each case based on criteria of biological plausibility, exclusion of other causes and, where possible, laboratory evidence of vaccine involvement. In most instances, however, the biological and laboratory features of the case do not allow the adverse event to be confidentially ascribed to the vaccine or excluded as being vaccine attributable. Under these circumstances, evidence of an increased risk of the event in a defined post-vaccination period must be sought, and this requires information on the incidence of events outside the post-vaccination risk period.
Controlled epidemiological studies of vaccine safety

There are a number of methods for conducting controlled epidemiological studies to assess the relationship between vaccination and clinical conditions suspected of being causally associated. All have the same requirement, namely that ascertainment of the conditions studied should be unbiased with respect to vaccination history. The methods can either provide estimates of the incidence of events in defined post-vaccination periods relative to the age-adjusted background rate, or the risk in vaccinated compared with unvaccinated individuals. When vaccine uptake rates are high, it may not be possible to make unbiased comparisons between vaccinated and unvaccinated cohorts, since those that remain unvaccinated are likely to be an atypical subset of the population. Alternative, ecological approaches (see below) may be necessary under such circumstances.

The classic post-licensure epidemiological methods for investigating causal associations are the cohort and case-control methods. Cohort studies must be very large in order to have sufficient power to detect rare vaccine adverse events and may, therefore, be impractical as a prospective undertaking. Retrospective cohort studies using data sets already assembled for other purposes can be used instead (Ray and Griffen, 1989), although the ability to account for the effect of important confounding variables may be limited by the available data. Furthermore, when using retrospective cohorts a clear distinction must be made between an exploratory study undertaken as a hypothesis-generating exercise and a study undertaken to test an explicit *a priori* hypothesis. Ideally, exploratory analyses should be undertaken with a view to conducting a formal hypothesis-testing study if evidence of a significantly increased risk is found in a particular post-vaccination period. If sufficiently large, the data set could be split into two, with half used to conduct an exploratory analysis and the other half used to test any hypotheses so generated. Although this approach should allow the identification of statistically significant effects that have arisen by chance (a type I error), it cannot overcome the effect of bias that may be inherent in the way the data set has been collected and that results in confounding of vaccination status and the adverse event.

The large linked databases from the Health Maintenance Organizations (HMOs) in the USA have recently been used to conduct a number of cohort studies to test hypotheses about the risk of vaccine adverse events in defined post-vaccination periods, e.g. febrile seizures after whole-cell pertussis or MMR vaccines (Barlow et al., 2001), or asthma exacerbations after influenza vaccine (Kramarz et al., 2000). Where possible, potential confounding factors were adjusted for in the analyses, as for example in the asthma study where the unadjusted analysis showed evidence of a significantly increased risk of an exacerbation within 2 weeks of vaccination but this disappeared after controlling for asthma severity (Kramarz et al., 2000). An example of using the HMO data sets for exploratory analyses is the investigation of the temporal relationship between OPV and intussusception. This was undertaken following confirmation of an increased risk of intussusception in the week after rotavirus vaccine to investigate whether this might be a generic problem with live oral virus vaccines (Andrews et al., 2001). Another example of an exploratory analysis with the HMO data set is the investigation of the relationship between cumulative thimersal exposure in the first year of life and developmental delay (http://www.cdc.gov/nip/vacsafe/concerns/thimerosal/joint_statement_00.htm). In both cases, marginally significant results in one of many analyses generated hypotheses that required formal testing in independent data sets. In each case the hypothesis generated by the exploratory analysis was not confirmed (Andrews 2001; Miller, 2002).
Case-control studies require smaller numbers than cohort studies but are subject to the same confounding with respect to acceptance/avoidance of vaccination and the putative adverse event. In addition, they may be subject to additional biases introduced by the selection of controls. For studies involving pediatric vaccines, close matching on date of birth is essential, as they are given within tight age ranges in the first and second years of life. For a fixed number of cases the power of a case-control study only approaches that of a cohort study with multiple controls per case. However, selection and matching of controls can be time consuming and, although an increase from one to two controls gives a fairly large increase in power, there are diminishing returns for more than three controls per case. In one of the most well-known case-control studies of adverse vaccine events, the National Childhood Encephalopathy Study of DTP vaccines, only two controls were selected for each case, with date of birth matched within 1 month of that of the case (Miller D *et al*., 1993).

A case-case control study nested within a cohort study is sometimes undertaken if relevant confounders have not been measured for the entire cohort or if information on vaccination status has not been collected. Identification of subjects from a cohort should minimize selection bias between cases and controls. A recent example of a nested case-control study was the study of the risk of multiple sclerosis after exposure to hepatitis B vaccine in two large cohorts of nurses in the USA who had been followed up for a number of years as part of a nurses’ health study (Ascherio *et al*., 2001). The combined size of the cohorts was nearly a quarter of a million among whom 192 women with multiple sclerosis were identified. Five healthy controls and one ill control with breast cancer were randomly selected from the cohorts after matching on year of birth and study cohort and, for the cancer patients, date of diagnosis. Information on covariates that could be confounders for risk of multiple sclerosis, such as latitude of birth, was obtained, as well as covariates that could affect likelihood of hepatitis B vaccination, such as type of nursing job. No evidence of an increase in the risk of multiple sclerosis after hepatitis B vaccination was found.

Because of the logistic problems associated with large cohort studies, and the difficulties of ensuring adequate control of confounding factors in both cohort and case-control studies, alternative epidemiological methods have been employed for investigating vaccine safety issues (Farrington, in press). These require data collection only on cases of the putative adverse event and are not only less labour intensive but can avoid some of the potential biases in cohort and case-control studies. As with the cohort and case-control methods, case ascertainment must be independent of vaccination history. Two ‘cases only’ methods have been used that can provide relative risk/incidence measures, namely the case-crossover and self-controlled case series methods.

The case-crossover method was developed to investigate the effect of transient exposures on the risk of acute events (Maclure, 1991) and has frequently been used for studying the impact of potential triggers on the risk of myocardial infarction (Maclure and Mittleman, 2000). It can, under certain circumstances, also be used for investigating vaccination risks (Farrington, in press). In a case-crossover vaccine study, vaccinations for each individual are ascertained in a defined time period immediately prior to the adverse event and in one or more earlier control periods of the same duration. This produces, for each case, a matched set of exposure variables corresponding to the event and control periods, which may be analysed as in a case-control study. A case-crossover design was recently used to investigate the effect of hepatitis B on the risk of relapse in multiple sclerosis in the subsequent 2 months (Confavreux *et al*., 2001). Four 2 month periods prior to the risk period were used as control periods. Each period was classified as ‘exposed’ if vaccination occurred within it,
and ‘unexposed’ otherwise. This gave an odds ratio of 0.67 (95 per cent confidence intervals 0.20, 2.17) for relapses 2 months after hepatitis B vaccination. The authors concluded that there was no evidence that vaccination increased the short-term risk of relapse.

The strength of the case-crossover method is that it does not require separate controls and that, by matching time periods within individuals, all individual-level confounders such as social class, geographic location, underlying state of health, etc. are automatically controlled for. However, the method has limited application for investigating the risk of adverse events after paediatric vaccines, since it requires the underlying probability of vaccination to be the same in the prior control and subsequent risk intervals. This is unlikely for vaccines such as DTP and MMR that are given within narrow age ranges in the first and second years of life, and where the adverse events likely to be temporally associated with these vaccines are also highly age dependent, e.g. febrile convulsions or onset of autism. The case-crossover design is also not suitable for use with seasonally administered vaccines (Farrington, in press).

The self-controlled case series (SCCS) method overcomes these limitation and was specifically developed in the early 1990s to allow rapid, unbiased estimation of the incidence of events in putative risk periods after various paediatric vaccines relative to the age-adjusted background incidence (Farrington et al., 1996, in press; Andrews, 2001). The SCCS method uses cases as their own controls, but, unlike the case-crossover method, derives from cohort rather than case-control logic. In particular, ages at vaccination are regarded as fixed, and the random variable of interest is the age at adverse event, conditionally on its occurrence within a predetermined observation period (Farrington, in press). In the SCCS method, like the case-crossover method, individual-level confounders are corrected for because individuals are matched to themselves, thereby eliminating one of the sources of bias in cohort and case-control approaches. As with the cohort method, age effects must be strictly controlled for in the statistical model. The power of the SCCS method is nearly as good as that of a cohort study when vaccine uptake is high and risk intervals are short, and it is superior to that of a case-control study (Farrington et al., 1996).

The comparative features of the cohort, case-control and SCCS methods are summarized in Table 14.2. Because the experience of an entire population is captured in a cohort study it provides both relative and absolute incidence estimates, whereas the case-control and SCCS methods provide relative incidence measures only. However, if other data are available to derive the incidence of the event in the population and if the proportion of all cases in the population that have been captured in the case-control or SCCS study can be estimated, and the vaccination coverage in the study population is known, then absolute and attributable risk estimates can be derived (Andrews, 2001). For example, in a study of hospital-admitted febrile convulsions after MMR vaccine given in the second year of life, a relative incidence of 3.04 (95 per cent confidence intervals 2.27–4.07) for convulsions in the 6–11 day post-vaccination period was found using the SCCS method (Farrington et al., 1995). The attributable fraction (67 per cent) was converted into absolute and attributable risks (1 per 2000 and 1 per 3000 respectively) based on estimates of the number of doses of MMR vaccine given in the second year of life in the population from which the study cases arose and on assumptions about the completeness of ascertainment of the cases of febrile convulsion in the study population (Farrington et al., 1995). These SCCS risk estimates were later confirmed by a cohort study using a large linked database in the USA (Barlow et al., 2001).

\(^1\)In a case-control study the odds ratio approximates to the relative risk for rare events.
The SCCS method has now been employed in a number of vaccine safety studies (Farrington et al., 1995, 2001; Taylor et al., 1999; Andrews et al., 2001; Miller et al., 2001, 2003; Sardinas et al., 2001). In some, the results have been directly compared with those generated by the cohort or case-control method (Kramarz et al., 2000; Murphy et al., 2001). The study that investigated whether influenza vaccine given to asthmatic children caused asthma exacerbations in the 2 weeks following vaccination did not show an elevated relative incidence using the SCCS method, whereas the cohort analysis without adjustment for asthma severity did (Kramarz et al., 2000). This illustrates the ability of the SCCS method to control for individual confounding variables without explicitly measuring them (Andrews, 2001). In a study of the risk of intussusception after rotavirus vaccines, the relative incidence estimates from an SCCS analysis were higher than from the case-control analysis study, indicating that the latter had probably underestimated the vaccine-attributable risk due to incomplete adjustment for confounding variables (Andrews, 2001; Murphy et al., 2001).

However, as stated above, the cohort, case-control and SCCS analysis methods all have a common limitation, namely that when vaccination coverage is high and hypotheses about ‘ever vaccinated’ as opposed to ‘vaccinated within a critical period prior to onset of putative adverse event’ require testing, none of the analytic methods can adequately control for the bias that is likely to arise from confounding of acceptance/avoidance of vaccination and the putative adverse events. Under these circumstances, recourse to ecological approaches may be necessary.

### Ecological Studies of Vaccine Safety

A vaccine safety study can be described as ecological if it compares the incidence of adverse events in populations with different vaccine exposures without obtaining information on vaccination at the individual level. Groups in the analysis are typically geographically or...
temporally defined and, if valid comparisons are to be made between them, convincing arguments should be advanced that such geographical/temporal differences are unlikely to have affected the comparison of adverse event rates.

Vaccination campaigns conducted within a short period of time in one population offer a unique opportunity for powerful ecological studies of vaccine safety. For example, da Silveira et al. (1997) used the acute flaccid paralysis surveillance established for the poliomyelitis eradication programme to investigate the hypothesis that measles vaccine causes GBS within 42 days of vaccination. The interval of 42 days was based on that observed with GBS and swine flu vaccine for which a causal association had been established. Data on cases of acute flaccid paralysis that met the clinical and laboratory criteria for GBS were obtained for the period 1990–94 from four South American countries where mass measles immunization campaigns were conducted for a single month in 1992–93. The number of GBS cases in the risk period (1 month plus 42 days, counting from the day the campaign started) was compared with that in the non-risk periods between 1990 and 1994. No excess was found, the observed number being 97, compared with 92 expected in any 72 day period. The authors concluded that there was no evidence of a causal link between measles vaccination and GBS and that the negative evidence was sufficiently strong to allow removal from the measles vaccine product insert of any mention of an association with GBS.

A similar ecological study was carried out with MMR vaccine (Dourado et al., 2000) to confirm the association reported elsewhere (Miller et al., 1993) that the Urabe mumps vaccine strain causes aseptic meningitis. The study took advantage of a 2 week mass immunization campaign in children aged 1–11 years with a Urabe-containing MMR vaccine that began in mid August 1997. Cases of aseptic meningitis were ascertained using standardized criteria from referrals to specialist hospitals for infectious diseases for the period March to October 1997. The weekly frequency of cases demonstrated a marked peak in incidence following the start of the vaccination campaign, confirming the causal association reported elsewhere and providing similar risk estimates.

As can be seen, ecological studies in which a brief pulse of vaccination is applied to a population can provide compelling evidence for or against a causal association. Other ecological approaches involving comparisons of secular trends in vaccine uptake and the incidence of the putative adverse events provide much weaker evidence, since a correlation cannot establish causality. If a correlation is found in an ecological analysis, then this may generate hypotheses that can be tested in more robust epidemiological studies. Although an ecological correlation cannot establish a causal relationship, lack of a correlation may provide compelling evidence against it. For example, the hypothesis that certain vaccines given after the age of 2 months increase the risk of insulin-dependent diabetes (IDDM; Classen and Classen, 1997) has been tested in a number of ecological studies by comparing trends in the incidence of IDDM in paediatric populations before and after the addition of new vaccines; no correlations have been found (The Institute for Vaccine Safety Diabetes Workshop Panel, 1999). Another example is the hypothesized causal relationship between MMR and autism, which, it was argued, was responsible for the substantial increase in prevalence of diagnosed autism both in the USA and the UK in the past two decades (Wakefield, 1999). However, if MMR is responsible, then there should be a close temporal correspondence between autism prevalence and MMR uptake by birth cohort. None of the ecological studies conducted to date has shown such a correlation (Gillberg and Heijbel, 1998; Dales et al., 2001; Kaye et al., 2001; Sardinas et al., 2001).
Conclusions

Sustaining public confidence in vaccination programmes has emerged as a major challenge in recent years, with a number of allegations about vaccine safety hitting the headlines in different countries. Whatever the inherent biological plausibility of a new claim about a vaccine side effect, it is essential that it is investigated rapidly and thoroughly. New statistical methods, combined with the availability of large linked databases, has greatly facilitated this process. However, detection and investigation of effects that may occur decades after vaccination remains problematic, particularly when vaccine coverage is high. Under these circumstances, ecological analyses may provide a useful methodological tool. If laboratory evidence is used to support an argument for causality then stringent criteria must be applied to such evidence. Finally, when vaccine-attributable adverse effects have been identified, it is important that the risk from the vaccine is placed in the context of the risk from the disease so that an informed decision can be made by the individual and those charged with deciding national vaccination policy.

References


