



Mechanisms Underlying Adverse Reactions to Vaccines

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Summary

A broad spectrum of adverse events is reported following human vaccination but such reactions are considered to be relatively rare. A variety of mechanisms has been proposed to account for such adverse events. These most commonly relate to the actual process of vaccination and range from the vagal reaction associated with anxiety about needle injection, to use of an inappropriate site of administration, or infection of the healthcare worker by accidental injection during needle-capping. Other adverse events directly associated with the vaccine include reversion to virulence of attenuated vaccine strains of organisms, or contamination of the vaccine product. Adverse events may involve immune-mediated phenomena triggered by exposure to the microbial or other components of vaccines. These include: classical IgE-mediated type I hypersensitivity reactions, and immune-complex type III hypersensitivity (Arthus) reactions. Such reactions may be localized or systemic in nature. A variety of autoimmune reactions has been suggested to be triggered by vaccination, but in general the evidence for such associations remains largely anecdotal. Finally, many reported adverse events are simply chance instances of infection or disease onset around the time of vaccination and are not causally associated with administration of vaccine.

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Introduction

This overview focuses on the main mechanisms leading to the occurrence of suspected adverse events (SAE) following vaccination. Four categories of SAE have been reported to occur in association with vaccination: those induced by the injection process, those relating to a direct action of the vaccine components, those reflecting an indirect immune-mediated process and those which are due to poorly understood or unknown mechanisms.

Adverse Effects Directly Induced by the Vaccination Process

The Injection Process

The most frequently reported adverse event related to human vaccination is a vagal reaction induced by apprehension and anxiety related to the injection process. This can occur before, as well as after, vaccination and

typically occurs among adolescents and young adults. It often leads to a fall and subsequent injury (e.g. broken teeth, head trauma), which may potentially have serious consequences. Such reactions often occur while queuing, with anxiety building up while waiting for the injection. They may also occur after vaccination, in which case an important differential diagnosis is an anaphylactic reaction. Fainting due to a vagal reaction usually happens in the first 5 min before or post-vaccination, which is earlier than would be typical for an anaphylactic reaction.

Another common direct SAE occurs as a consequence of improper injection technique. For example, injection into the buttocks is not recommended as the vaccine may be delivered into adipose tissue where there is limited ability of the immune system to process the vaccine. This route of delivery also carries a risk of sciatic nerve lesions, especially in infants. In patients with bleeding disorders, intramuscular injection may precipitate haematoma formation.

A major concern is that type of SAE reflecting the inappropriate reconstitution of lyophilized vaccines,

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for example by mistaking a local anaesthetic for the vaccine buffer, where these may be stored in the same refrigerator. Finally, unsafe or accidental injections may occur, mostly among healthcare workers (so-called “needle recapping” injuries). These are a frequent cause of transmission of blood-borne agents (e.g. HIV, malaria). Vaccine microbial contamination due to the unsafe disposal or reuse of disposable needles and instruments is also a significant public health concern.

The Replication of Live Vaccines

An SAE may occur directly through the excess replication of a live vaccine. This is usually due to insufficient attenuation of the vaccine strain. For example, there is a small risk of aseptic meningitis following use of live mumps vaccine of particular strains. This risk ranges from one case per thousand to one per million doses. A further example is the risk of adenitis with the use of vaccines containing various strains of BCG. These observations have led to the withdrawal of the vaccines with the highest risk, and the selection of less virulent strains. However, a less reactogenic vaccine is sometimes also less efficient. For example, the mumps vaccine (Urabe strain) that was once available in Europe was much more efficient than that which is currently available.

A live vaccine strain may also revert to having the virulence of a wild-type viral strain. This risk is estimated at approximately one case of paralytic poliomyelitis per 750,000 doses for the first injection of live polio vaccine. This risk is virtually negligible in countries with a high incidence of polio but becomes unacceptable as polio is controlled. Countries thus change their policy when they reach a certain socio-economic level, abandoning the use of the oral (live) vaccine in favour of the injectable (inactivated) vaccine. At present, discussion is taking place at an international level because of the imminent success of worldwide poliomyelitis eradication. The nearer this target, the less acceptable the risk of vaccine-associated paralytic poliomyelitis becomes.

Adverse Effects Directly Caused by Vaccine Components

The Antigen

There are numerous examples of SAE related directly to vaccine components. For example, toxin-based vaccines may undergo insufficient or inappropriate detoxification during the manufacturing process. Minute amounts of residual tetanus toxin in a final toxoid preparation would have a most deleterious effect on the vaccinated individual. In the case of live vaccines, adverse effects may be the direct result either of “nor-

mal” replication of the vaccine strain, or of insufficient ability of the host to control replication. Normal replication allows the pathogen to grow and persist within the host, which may trigger an inflammatory reaction. Local suppuration and adenitis are therefore considered as a normal reaction to BCG administration in a limited proportion of children, and can persist for weeks to months as a localized skin lesion. The strain, dose and injection technique all play a role in the severity and prevalence of this reaction, but there is no evidence of an increased risk of vaccinating infants at birth with BCG as compared with later in life.

Immune deficiency of the host may result in insufficient control of replication of the vaccine strain. Consequently, live vaccines should not be used if immune deficiency is suspected. In this respect, it is often questioned whether subjects with immune compromise (e.g. infants, elderly patients, pregnant women) should be vaccinated. In neonates, vaccine safety is vaccine-dependent. For example, although there is a normal response to oral polio vaccine and to BCG at birth, there is a higher risk of encephalitis when yellow fever vaccine is injected before 6 months of age. There are also many concerns regarding the exposure of pregnant women to live vaccines, and efforts are made to avoid such an exposure. Nevertheless, evidence is accumulating showing that live-attenuated vaccines are safe in pregnant women, including the rubella vaccine which has been shown to be non-teratogenic when accidentally administered to pregnant women. Even if not recommended, such vaccination has proven to be safe.

Other Vaccine Components

In addition to antigen, vaccines generally include a range of other components such as adjuvants, preservatives or stabilizers. There is little evidence that these may be directly toxic to humans. Aluminium salts are currently the only authorized adjuvant for infant vaccines. Thiomersal, a mercury derivative, used as a vaccine preservative, has not been reported to have direct adverse effects. If SAE occur in relation to these vaccine components, the mechanism is generally considered to be indirect; i.e. via the host response to the vaccine components.

Adverse Effects Due to the Host Immune Response

Local Inflammatory Reactions

A localized inflammatory response following immunization is a frequently reported adverse effect, and is mainly observed with adjuvanted inactivated vaccines. The large local antigen deposit is evident on histological examination of such reaction sites. This results in

Toll-like receptor (TLR)-mediated recognition of danger signals, leading to a marked infiltration of macrophages and/or dendritic cells (antigen-presenting cells) which initiate a local inflammatory reaction. Different vaccine formulations incorporating the same antigenic component may induce different levels of local reactions. Both the antigen and the adjuvant play a role in the severity and the duration of the inflammatory reaction.

Local reactions may be broadly divided as to whether or not they induce pain. A painful local reaction is the result of either an antigen/adjuvant TLR-induced inflammation, or of an Arthus reaction. The latter is characterized by residual antibodies still present in the host due to previous sensitization. The new injection of this sensitized individual results in antigen deposition at the site of injection, which is recognized by residual antibodies leading to the formation of immune complexes at this site. This mechanism is thought to underlie the pain response often experienced following a booster shot of tetanus vaccine.

Other spectacular local reactions may be totally painless. In such reactions, fluid extravasation takes place, resulting in oedema, without signs of allergy or of excess antibody responses. This type of reaction is well-described after immunization with diphtheria–tetanus–acellular pertussis (DTPa) vaccines.

Systemic Inflammatory Reactions

Systemic inflammatory reactions are not uncommon and presenting signs may include fever, irritability, nausea, vomiting and myalgia. Such reactions usually occur within 24–48 h following the injection of killed vaccines, and resolve within 72 h. In the case of live vaccines, the reaction generally occurs after an incubation period of 14–21 days.

The systemic effect of live vaccines was shown in a twin study conducted in Finland, where one twin received a measles–mumps–rubella (MMR) vaccine at 1 year of age while the control twin received a saline injection. Six weeks later the MMR-vaccinated twin received a saline injection whilst the control was vaccinated with MMR (Virtanen *et al.*, 2000). Twenty per cent of the children that had received the vaccine developed a systemic reaction (pyrexia) within 12 days whilst only 10 per cent of the concomitant placebo group became feverish.

Five host factors may influence the development of inflammatory reactions to vaccines:

- I. *Age*: Independent of the vaccine, usually the younger the age, the weaker the reaction; with the exception of preterm babies.
- II. *Gender*: Inflammatory reactions are more common in females than in males.
- III. *Genetics*: Although genetic background is considered important, little data on candidate gene involvement are available.
- IV. *Previous infection*: Pre-existing antibodies may neutralize live vaccines, causing a lower reactogenicity to the second dose of live viral vaccines.
- V. *Previous vaccine doses*: A higher reactogenicity is observed with an increasing number of doses, because of stronger anamnestic cytokine responses.

Allergic Reactions

Allergic responses to vaccines are usually triggered by non-antigenic vaccine components such as gelatine or neomycin, such that the effect may occur following administration of the first dose of vaccine. The mechanism involved in this type of reaction is generally considered to be a classical type I hypersensitivity reaction involving an IgE-mediated response, causing urticaria, angioedema and anaphylaxis. The frequency of anaphylactic events varies with the type of vaccine. On average, it is estimated that such reactions occur in 0.65 cases per million doses (Bohlke *et al.*, 2003). The highest frequency reported is eight cases per million doses. This is still remarkably low, given the high number of components present in each vaccine.

Type IV delayed hypersensitivity reactions have also been reported but are generally considered to be harmless. These start 48 h after vaccination and peak between 72 and 96 h post-vaccination. They are typically observed with vaccines containing thiomersal in sensitized children and adults, and the occurrence of such an event is not a contraindication to further immunization. This reaction is becoming less frequent as mercury is being removed from modern vaccines. Other reported hypersensitivity reactions include erythema multiforme, which can be quite severe in children, and is triggered by a number of allergens, amongst which are included vaccine components.

Other Immune-Related Reactions

These include idiopathic and autoimmune responses. Vaccination may induce self-reactive antibodies, due to molecular mimicry between the vaccine antigen and an endogenous epitope. For example, several viral infections may induce autoantibodies to platelet surface glycoprotein, producing an idiopathic thrombocytopenic purpura. The incidence of such reactions varies and is reported to be approximately 1 in 6000 for measles virus, 1 in 3000 for rubella virus, and 1 in 30,000 for MMR vaccine (Miller *et al.*, 2001).

The best-documented example of a vaccine-associated autoimmune reaction was the occurrence of Guillain-Barré syndrome after mass vaccination of people with a swine influenza vaccine, during an

immunization campaign that took place in 1976–1977 in fear of an influenza pandemic that was suspected to originate from swine influenza. A number of vaccinees developed Guillain-Barré syndrome within 6 weeks of vaccination. The campaign ended in 1977, and no further cases were observed. There was no excess risk after 1977 with seasonal influenza vaccination.

Other unexplained reactions have been described with inactivated vaccines against viral pathogens. Measles vaccines in the 1960s were inactivated and very well tolerated. They did not induce any SAE and were transiently protective. However, approximately 10 years after immunization, when some subjects were exposed to the wild-type virus, they would develop an atypical disease that could be quite severe. The immune mechanism underlying this disease has recently been elucidated and the condition has also been reproduced in Rhesus monkeys (Polack *et al.*, 1999). Inactivated measles vaccines had induced short-lived neutralizing antibodies and a polarized Th2 CD4⁺ T cell response, without any anti-viral cytotoxic response. Antibodies that persisted were of low-avidity, non-protective, complement-fixing antibodies. Upon natural measles infection, the subject was not protected, and these antibodies generated an immune-complex disease with eosinophilic infiltration of the skin and lungs.

Adverse Effects Due to Unknown or Partly Understood Mechanisms

Several other immune-mediated diseases have been suggested to have been triggered by vaccination but mechanisms underlying these associations are poorly defined. There have been anecdotal suggestions that measles vaccination may trigger inflammatory bowel disease and autism, hepatitis B vaccine may trigger multiple sclerosis, aluminium adjuvant may be responsible for macrophagic myofascitis, *Haemophilus influenzae* b vaccine may trigger type I diabetes and that any vaccine may potentially initiate autoimmunity. However, none of these assertions is supported by unequivocal epidemiological evidence.

One of the most striking examples of such an SAE is the occurrence of intestinal intussusception attributed to the oral administration of a licensed Rhesus rotavirus vaccine (Rotashield®; Wyeth-Ayerst Laboratories, Philadelphia, USA) to infants. A total of 89 cases (either presumptive or confirmed) have been registered by the US Centers for Disease Control and Prevention. Most occurred within a week of vaccine administration. The estimated frequency of this event (within 1 week post-immunization) has been estimated at one in 10,000 doses. As a result, the vaccine has been

withdrawn from the market. The mechanism is still not fully understood.

The Healthy Infant Effect

Adverse events are frequently reported in temporal association with immunizations. As an example, respiratory infections are often reported after MMR immunization of 12-month-old infants. This was investigated by Finnish twin studies, in which the vaccinated group presented an increase in respiratory symptoms during the first week after vaccination. Several hypotheses could explain this observation, including vaccine-induced immunosuppression, overload of the immune system, and even autoimmunity, although this is a low risk phenomenon in early life. The Finnish study, however, came to a much simpler explanation as the placebo group showed exactly the same frequency of respiratory symptoms. The baseline incidence of respiratory symptoms in 1-year-old children is somewhere between 15 and 20 per cent. Since a child is vaccinated at a time when it is healthy, i.e. between two episodes of viral respiratory infections, it will return to the baseline of 15–20 per cent disease incidence within a week or so. This “well-baby effect” is a well-described effect, which may be challenging to explain to parents who mainly see that “their child got sick after the vaccination”.

Misleading Temporal Associations

As the infant vaccination schedule is relatively crowded, and since almost all babies are vaccinated, there is a reasonable chance that any event during the first 6 months of life may occur just before or just after a vaccination. If the event is post-immunization, the possibility that the vaccine will be blamed is high. These coincidences are unavoidable and temporal association of diseases and vaccination may be so misleading that to explain this is perhaps one of the largest communication challenges for paediatricians in relation to vaccination.

Over the years, several allegations questioning vaccine safety, which surprisingly differ according to countries, have occurred, none of which have been supported by scientific evidence. Examples of these include: the alleged association of pertussis immunization and brain damage in Sweden, the proposed linkage of MMR vaccination and autism in the UK, the suggested associations between hepatitis B vaccination and multiple sclerosis, and aluminium adjuvant and macrophagic myofascitis in France, and the proposed association between thiomersal and impaired neurodevelopment in the USA.

An initial temporal relationship between vaccination and disease onset leads to a tentative link between

cause and effect, whilst inadequate answers lead to persisting doubts among the public, causing irreversible damage to the image of vaccination and the vaccine program. One should thus emphasize that although a biological risk is never zero, the benefits of immunization far outweigh any potential risk and provide an optimal support to a healthy life.

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