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Adverse Vaccination Reactions in Animals and Man

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ABSTRACT

It was only possible because of vaccination that we were able to create a safe environment for us and animals/ pets. If it was not for rabies vaccination, we never would have kept dogs and cats as our companion animals as we do now, and we never would have been able to protect our domestic animals from diseases that not only reduce the productivity but may even be deadly. But the vaccines comes with their own adverse effects such as hypersensitivity reactions which occur due to some component of the infectious agent or one of its products; due to stabilizers like gelatin; due to adjuvants like aluminium hydroxide; due to preservatives like thiomersal; due to antibiotics like neomycin; and due to a biological culture medium like chicken embryo cells. Other adverse effects include autoimmune disorders like immune mediated hemolytic anemia, thrombocytopenia and neoplastic diseases like fibrosarcomas. Lack of efficacy, interference with diagnostic testing and other occasional suspected product-related issues have also been reported as adverse vaccination reactions. An absence of adverse reaction indicates that the immune system has not been stimulated but due to variability in the vaccines immune system, environmental conditions and the nature of the vaccine, sometimes there may be excessive stimulation of immune system thus causing serious reactions. The common reasons for occurrence of vaccine reactions are contamination of vaccines with extraneous chemical agents, failure to inactivate the vaccine organism in a killed vaccine, adverse vaccine reactions due to vaccine-induced immune suppression, adverse vaccine reactions due to excessive induction of cytokine release. Also other adverse reactions are due to human errors like administration at the wrong site or improper dilution of the vaccines, or improper storage or transportation of vaccines and thus can be minimized. Also some vaccine reactions occur due to simultaneous administration of different vaccines so is preventable. Due to a marked degree of underreporting and a bias toward more severe adverse reactions, proper data for the vaccine reactions is not available from field conditions, also due to limited number of animals used during vaccine trials, there is no accurate data even in controlled settings as to how much adverse reactions can be expected while administering a vaccine. To solve this problem post marketing surveillance for all the vaccines should be done which should involve four interrelated components, namely, data collection, analysis, interpretation, and timely dissemination. To tackle this problem of adverse vaccination reaction we can also go for double blind placebo trails as are done for drug testing in which comparison is done between vaccinated and unvaccinated group and not just one vaccinated group with other vaccinated group.

KEYWORDS: Vaccine, Adverse reactions, Allergy, Hypersensitivity, Immunosuppression, Man, Animals.

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INTRODUCTION

An Adverse event following immunization is any adverse medical occurrence which follows immunization and that does not necessarily have a causal relationship with the usage of the vaccine itself. The adverse event can be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. These are of 5 types, Vaccine product related reaction that are caused or precipitated by a vaccine which is because of one or more of the inherent properties of the vaccine itself. Example: Extensive swelling

of limb following DTP vaccination. Vaccine Quality defect related reactions that are caused or precipitated by a vaccine because of one or more quality defects of the vaccine product including its administration device as given by the manufacturer. Example: Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio. Immunization error related Reaction, that are caused by inappropriate vaccine handling, prescribing or administration and thus is preventable. Example: Transmission of infection by contaminated multidose vial. Immunization stress related reactions are due to anxiety of vaccine. Example: Vasovagal syncope during/following vaccination. Coincidental reactions are those events which occur after a vaccination has been given but are not caused by the vaccine components or its improper administration or psychological fear. They are naturally occurring diseases which happen to overlap along with vaccine schedule, mainly because vaccination are mostly carried out during early childhood and during this time illnesses are very common. Example: A fever occurs at the time of the vaccination (temporal association) but is in fact caused by malaria. Coincidental events reflect the natural occurrence of health problems within community with common problems being frequently reported.

Therefore, it is to be expected that occasionally adverse clinical signs will occur after animals have been vaccinated for reasons which maybe unrelated to vaccine administration. There are many reasons why many vaccines may induce adverse reactions in the animals, poultry and man; also it is important to differentiate true adverse vaccine reactions from other health adversities.

Why vaccine reactions occur?

Contamination of vaccines with extraneous chemical agents

A prominent example of this was when it was discovered that some lots of the live oral human poliomyelitis vaccine were contaminated with live simian virus 40 (SV40) in the 1950s (Pennisi, 1997; Shah and Nathanson, 1976). Millions of people were potentially exposed to live SV40 through administration of polio vaccine. There is no solid epidemiologic evidence till date that suggests that any adverse health effects can be attributed to exposure to this agent. The SV40 virus had not yet been discovered when the human polio vaccine was produced which raises the question of how can we test for all potential known and unknown viruses in each production lot of modified live virus vaccines. And this is one of the major reasons for vaccine failure and adverse reactions. There have been numerous examples when extraneous agents contaminate veterinary vaccines. Abortion and chronic wasting may be observed in cattle vaccinated with rota-corona vaccine contaminated with bovine viral diarrhoea (BVD) virus (Chauhan and Tripathi, 2002; Agrawal *et al*., 2004).Some examples of adverse vaccine reactions due to extraneous agents in **vaccines is presence of** Killed hog cholera virus in pseudorabies vaccine (Jensen, 1981), Live Mycoplasma in multiple live virus (MLV) veterinary vaccines (Thornton, 1986), Live border disease virus in Orf vaccine (Loken *et al*., 1991), Live bovine leukemia virus in babesiosis and anaplasmosis vaccines (Rogers *et al*.,1988), Live bovine viral diarrhea virus in hog cholera vaccine (Wensvoort and Terpstra, 1988), Live border disease virus in pseudorabies vaccine (Vannier *et al*., 1988), Live blue tongue virus in a canine vaccines (Evermann *et al*., 1994; Wilbur *et al*., 1994), Live bovine viral diarrhea virus in bovine vaccines (Lohr *et al*., 1983; Neaton, 1986). Similarly in poultry, there are many such heath problems associated with administration of vaccines (Singh and Chauhan, 1999).

Failure to inactivate the vaccine organism in a killed vaccine

A dramatic example of this cause of adverse vaccine reactions occurred with the killed poliovirus vaccine in people. Formaldehyde which was used to inactivate the poliovirus in the vaccine, failed to completely inactivate the vaccine virus (Gard and Lycke, 1957; Nathanson and Langmuir, 1963).This resulted in several cases of poliomyelitis in people that had received the vaccine. There have also been cases where formaldehyde failed to inactivate the foot-and-mouth disease virus (Beck and Strohmaier, 1987; King *et al*., 1981) and the Venezuelan equine encephalitis virus (Kinney *et al*., 1992) in their respective vaccines. In both of these cases the vaccine was shown to induce disease because of the lack ofcomplete inactivation of the virus by the formaldehyde (Brown, 1993). An example of a failure to completely inactivate a bacterial pathogen in a killed bacterin occurred when thimerosal was used to inactivate *Haemophilus somnus* in an *H. somnus* vaccine. The thimerosal failed to kill the *H. somnus* and almost half of the animals injected developed thromboembolic meningoencephalitis and died.

Adverse vaccine reactions due to residual virulence of vaccine organisms

Modified live vaccine organisms have been attenuated to have reduced virulence. The attenuation must be shown to be stable when passage through animals; therefore, reversion to virulence is thought to be a rare event. However, the attenuated vaccine strains may be capable of producing disease in immunosuppressed animals. Induction of disease by the vaccine organism has occasionally been reported when modified live virus (MLV) vaccines have been administered to healthy animals. However, it has occurred much more frequently when MLV vaccines are administered to unhealthy animals, by a non-recommended route of exposure, to animals younger than the intended age for use of the vaccine, or when the vaccine is used in other than the intended species. Examples of MLV vaccines occasionally causing disease in healthy animals of the recommended species without apparent predisposing causes include the induction of rabies

in dogs and cats after administration of an MLV rabies vaccine (Bellinger *et al*., 1983; Esh *et al*., 1982; Erlewein, 1981; Whetstone *et al*., 1984; Pedersen *et al*., 1978) and the induction of ovarian lesions and infertility in seronegative heifers administered MLV bovine herpesvirus 1 (BHV1) vaccine during estrus (Smith *et al*., 1990; Chiang *et al*., 1990; Miller *et al*., 1989; Van der Maaten *et al*., 1985). Since most heifers already have antibody to BHV1 due to either vaccination or previous exposure, this is thought to be a rare occurrence. An example of vaccine-induced disease resulting from administration of vaccine to unhealthy animals is the induction of encephalitis by MLV canine distemper virus vaccine in dogs infected with canine parvovirus (Krakowka *et al*., 1982). An example of adverse vaccine reaction after exposure of an animal to an MLV vaccine by a non-recommended route of exposure is the induction of clinical feline viral rhinotracheitis after inadvertent exposure by the intranasal route to an MLV vaccine that was intended for intramuscular administration only (Povey and Wilson, 1978). MLV vaccines that have been shown to be safe in older animals may not be safe in neonatal animals. An MLV BHV-1 vaccine induced fatal BHV1 infection in neonatal purebred Salers calves (Bryan *et al*., 1994). This may have been partially due to the breed of the animals since there are other reports that MLV BHV1 vaccines are apparently safe in neonatal calves (Schuh and Walker, 1990). There have been several examples of MLV vaccines inducing lethal disease when administered to a species other than the target species. An MLV pseudorabies virus vaccine produced fatal pseudorabies in lambs (Clark *et al*., 1984; Van Alstine *et al*., 1984). This occurred when a syringe that had been used to administer the pseudorabies vaccine to pigs was used without proper disinfection to vaccinate lambs with another vaccine 3 days later. The MLV canine distemper virus vaccine has been shown to induce canine distemper infection in gray foxes (Halbrooks *et al*., 1981), kinkajous (Kazacos *et al*., 1981), and lesser pandas (Bush *et al*., 1976). An MLV rabies vaccine has been shown to induce rabies in a pet skunk (Debbie, 1979). An MLV feline panleukopenia vaccine induced cerebellar hypoplasia when given experimentally to neonatal ferrets (Duenwald *et al*., 1971).Use of killed vaccines in cattle against the *Pasteurella multocida*and *P. haemorrhagica*may cause severe respiratory reactions due to the cytotoxic factor produced by *P. multocida* which replicate in the presence of specific IgG antibodies (Chauhan and Tripathi, 2002; Chauhan and Sharma, 2010).

Adverse vaccine reactions due to vaccine-induced immune suppression

An MLV bovine viral diarrhea (BVD) virus vaccine has been shown to suppress neutrophil function and lymphocyte blastogenesis in cattle (Roth and Kaeberle, 1983). This correlates with the observation that cattle tend to be somewhat more susceptible to bacterial pneumonia after administration of MLV BVD vaccines, especially if the animals are stressed at the time of vaccination. Several commercially available canine vaccines have been shown to be capable of inducing lymphopenia and suppressing blastogenesis of peripheral blood lymphocytes (Phillips *et al*., 1989; Mastro *et al*., 1986; Kesel and Neil, 1983). Lymphopenia and suppression of blood lymphocyte blastogenesis must be interpreted with caution, however, because it may only be an indication of changes in lymphocyte trafficking between the blood and lymphatic systems rather than an indication of depressed lymphocyte function. Vaccination with an MLV BHV1 vaccine has been shown to exacerbate the lesions of infectious bovine keratoconjunctivitis after experimental intraocular challenge with *Moraxella bovis* (George *et al*., 1988).

Adverse vaccine reactions due to excessive induction of cytokine release

Interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF) are potent proinflammatory cytokines that are released by macrophages and other cells in response to infection, endotoxin and other bacterial components, and some vaccine adjuvants. These proinflammatory cytokines can induce a wide range of clinical signs. They may induce acute inflammation at the local site of production, they may induce rapid synthesis and secretion of acute phase proteins by the liver, they may act on the hypothalamus to induce fever and malaise, they may reduce rate of gain and feed efficiency, and in sufficiently high concentrations they may induce hypoglycemia, reduce cardiac output, cause hypovolemic shock, and cause disseminated intravascular coagulation. Lipo-polysaccharide (or endotoxin) from gram-negative bacteria is one of the most potent inducers of the proinflammatory cytokines (Cullor, 1994; Ellis and Yong, 1997; Galanos and Freudenberg, 1993). A number of other bacterial components like Lipopolysaccharide, Lipid A, Porins, Muramyl peptides, Peptidoglycan, Mycoplasma lipoproteins, Teichoic acid, Lipoteichoic acids, Lipoarabinomannans, Protein A, Super antigens have also been shown to induce proinflammatory cytokine production (Erdos *et al*., 1975; Henderson and Wilson, 1995; Allison and Eugui, 1995). These components are generally the most active if they are released from the degraded bacterial cell. Killed bacterins that contain excessive amounts of these bacterial components can induce clinical signs due to excessive induction of cytokine release. This is more likely to occur if multiple killed bacterins are administered at the same time and if these bacterins contain adjuvants that also induce cytokine release. The production of small amounts of proinflammatory cytokines is beneficial to the induction of a protective immune response. However, overproduction of the proinflammatory cytokines can have mild to very severe adverse side effects.

Hypersensitivity responses to vaccine antigens

Animals may develop any of the four types of immune-mediated hypersensitivity reactions to vaccine antigens. Systemic anaphylaxis due to type I (immediate type) hypersensitivity is the most dramatic type of adverse vaccine reaction. This can occur as a result of the induction of IgE class antibody to essentially any component of a vaccine (Bonin *et al*., 1973; Wilson *et al*., 1968; Erdos *et al*., 1975). As with all of the hypersensitivity reactions, the animal will not react on first exposure to an antigen (unless it has received passive antibody responsible for the reaction). It will only react after there has been sufficient time to produce the sensitizing antibody or memory T cells. A local type I hypersensitivity reaction may occur due to IgE induced against infectious agents by the vaccine. Immunization against bovine respiratory syncytial virus under experimental conditions was shown to induce IgE antibodies specific for BRSV which apparently contributed to the development of symptoms following aerosol challenge with BRSV (Stewart and Gershwin, 1989 a,b).

Vaccine-induced type II (cytotoxic type) hypersensitivity reactions can occur when vaccines are used that contain normal cell antigens. For example, vaccines that contain erythrocyte antigens may induce anti-erythrocyte antibodies leading to immune-mediated hemolytic anemia. Type III (immune complex type) hypersensitivity can occur when circulating antibody specific for vaccine antigens is present at the time of vaccination. This can lead to an Arthus reaction at the site of injection due to complement fixation and neutrophil recruitment to the site. This mechanism is commonly responsible for the local inflammatory reaction at the site of injection, especially when administering booster vaccinations with killed vaccines. Sometimes, hypersensitivity can be one component of a more complex adverse vaccine reaction. Antibody induced by the vaccine may lead to immune complex type hypersensitivity reactions after the animal becomes infected when the antibody binds to replicating infectious agents. Examples include anterior uveitis and corneal edema (blue eye) after vaccination with canine adenovirus (Carmichael *et al*., 1975; Wright, 1976) and the sensitization to the effusive form of feline infectious peritonitis after vaccination with experimentally killed vaccines (Pedersen and Black, 1983) . Sometimes, hypersensitivity may be one component of a more complex adverse vaccine reaction. Bacterins for *Pasteurella hemolytica* which were marketed and widely sued for several years were of marginal efficacy and were even capable of increasing the severity of lesions in animals either experimentally (Wilkie *et al*., 1980) or naturally exposed (Bennett, 1982) to the *P. hemolytica*. There are at least two hypothesized mechanisms by which the immune response induced by the bacterin could potentiate pneumonia after *P. hemolytica* challenge. First, the high concentration of complement-fixing antibody induced by vaccination with a bacterin could rapidly activate complement if a large number of *P. hemolytica* organisms were introduced into the lung either naturally or artificially. This could cause a type III hypersensitivity response leading to acute inflammation in the lung and severe pneumonia. Second, antibody against cell surface antigens will opsonize the *P. hemolytica* in the lung and enhance phagocytosis by alveolar macrophages and neutrophils. Because there may be insufficient leukotoxin-neutralizing antibody or cell-mediated immunity to activate phagocytes, the bacteria present in the alveoli and ingested by phagocytes are not efficiently killed and may produce leukotoxin that could destroy the phagocytes. This destruction would cause the phagocytes to release their hydrolytic enzymes into the lung.

Vaccine-induced triggering or exacerbation of hypersensitivity disease to non-vaccine antigens

In the last few years concern has been expressed that vaccination may trigger or exacerbate autoimmune disease or allergies (hypersensitivities), especially in dogs and cats. Vaccination has been shown to augment production of IgE antibody to pollen in inbred atopic dogs (Frick and Brooks, 1983). Remember that animals with allergies or autoimmune diseases are not healthy animals, and that vaccines are only recommended for use in healthy animals.

Vaccine-induced neoplastic disease

In recent years, an increased incidence of fibrosarcoma occurring at sites commonly used for vaccination in cats has been observed (Hendrick *et al*., 1992, 1994; Kass *et al*., 1993). The causal relationship and mechanistic basis for vaccine-associated fibrosarcomas in cats has not been firmly established (Ellis *et al*., 1996). MLV BVD vaccine triggering mucosal disease in persistently infected cattle Shortly after MLV BVD vaccines were introduced, it was recognized that a very small percentage of cattle developed a syndrome 7-20 days after vaccination that closely resembled BVD mucosal disease (Lambert,1973; Peter *et al*., 1967). Based on the current understanding of the pathogenesis of mucosal disease (Bolin *et al*., 1985; Brownlie *et al*., 1984) this was almost certainly due to the cytopathic BVD virus in the vaccine triggering mucosal disease in calves that were immunotolerant to, and persistently infected with, a noncytopathic BVD virus. The mechanistic basis for the induction of the lesions of mucosal disease is not clearly understood. This unique syndrome is primarily due to abnormalities in the animal rather than to a defect in the vaccine.

Adverse reactions due to multiple vaccines administered concurrently

Vaccines are tested for safety and efficacy when administered to healthy animals in the formulation in which they are packaged to be sold. Vaccines are not required to be tested for safety and efficacy when administered concurrently with other vaccines. This would not be practical since there

are too many possible vaccines that may potentially be used in combination. An example of a safety problem that occurred when two different vaccines were administered concurrently involved a newly developed MLV canine coronavirus and parvovirus vaccine given at the same time as an MLV canine distemper-hepatitis virus vaccine. The evidence indicated that the other MLV components allowed the canine coronavirus in the vaccine to induce neurologic disease in some vaccinated animals (Wilson *et al*., 1986).

COMMON VACCINE REACTIONS

Vaccine reactions can generally be categorized as either systemic or local. Systemic reactions include type I hypersensitivity or anaphylaxis, type III complex-mediated hypersensitivity, diluent and contamination problems, and reactions due to endotoxins. Local site reactions include type I hypersensitivity, type IV cell-mediated (delayed type hypersensitivity), reactions to adjuvants such as granulomas and possibly even cancer (Hendrick *et al*., 1992), diluent and contamination related problems, and faulty administration techniques. The failure of a vaccine to protect against the disease for which it is intended can also be considered as an adverse reaction. In an study conducted by Yeruham in 2001, cattle of a dairy farm were observed after annual FMD vaccination and three types of skin lesions i.e., pruriginous urticaria; numerous wheals (3–20 mm in diameter, covering most of the body) and exudative and necrotic dermatitis were seen. The affected areas exhibited multifocal hair loss. In addition, leg oedema and vesicles on the teats occurred. These lesions were seen eight to twelve days post-vaccination, and persisted for three to five weeks. Around 4.2% mean loss of body weight and lymphadenopathy was also seen. Also there was a reduction in milk production. Pyrexia and other clinical signs characteristic of FMD were not observed. The frequency of these reactions was highest among adult cows and most severe in the high-yielding cows (Yeruham *et al*., 2001). A decline in motility and viability of sperms and increase in abnormal sperm count in bulls vaccinated with polyvalent FMD vaccines is observed. Similar effect are seen when black quarter *(Clostridium chauvoei)* and FMD vaccines are used simultaneously. Also if combined FMD-rabies vaccine is used more frequently, there may be loss of hairs and scrotal oedema after 8-20 days of vaccination in bulls (Yaruham *et al*., 2001;Chauhan and Sharma, 2010). Also high mortality is seen in calves after two weeks of immunization with live attenuated schizont *Theileria annulata* vaccine. This may be due to a high dose of immunogen in immunologically or MHC-mismatched recipients. Immunized animal may show long inter-oestrus interval characterized by high progesterone level and persistent corpus luteum (Chauhan and Tripathi, 2002). In lambs congenital abnormality of the brain is seen after vaccination of pregnant ewes with Bluetongue virus vaccine (Chauhan and Tripathi, 2002). Also vaccine administration in pregnant animals has shown to cause abortions.

Local Site Reactions

Local site reactions can include erythema, oedema, swelling and urticaria at the site of injection. These signs can appear within 30 minutes of the injection or may take 10 to 14days to manifest, depending on the pathogenesis of the condition. Erythema, edema and pain at injection site are often observed after typhoid, varicella zoster and typhoid vaccination in humans (Sur *et al*, 2009; Kuter *et al*., 1991; Wassilak, 2008). The local reaction rate was reported to be appreciably higher in women than in men in case of typhoid vaccination and the incidence among women increased with age (Myers *et al*., 1982; CDC, 1996). After Japanese encephalitis vaccination in humans, pain, redness, induration, swelling and tenderness is observed in about 40% of adult vaccine recipients (Dubischar-Kastner *et al*., 2010) and in approximately 10 % of children aged 1-3 years when receiving their primary course of vaccination (Kaltenboeck *et al*., 2010).

1. Type I Hypersensitivity

In type I hypersensitivity, the antigen reacts with antibody (IgE and some minor IgG subclasses) that is specifically bound to the surface of mast cells or basophils. This interaction initiates degranulation of the mast cells and release of vasoactive amines (including histamine) and other physiologically active mediators, leading to the signs of inflammation, which are observed normally within 2hours after infection (Trinca, 1979; Tizard, 1982; Roitt, 1984; Perryrnan, 1989). The antigen can be either the active ingredient or other components of the vaccine. For example, a component of a number of live viral vaccines is foetal calf serum. Animals can be sensitized to foetal calf serum by prior exposure to bovine milk, and this can lead to a type I hypersensitivity reaction after the initial vaccination. Anaphylaxis and allergic reactions are often seen after vaccination with anthrax vaccine (CDC, 2000; Storm *et al*., 2002), A case of hypersensitivity pneumonitis following anthrax vaccination is also reported (Timmer *et al*., 2002).

2. Type IV Cell-mediated (delayed-type) Hypersensitivity

In this type of hypersensitivity T-lymphocytes are stimulated by contact with macrophage-bound antigen to release lymphokines that mediate the inflammatory response. The reaction is characterized by erythema and induration, which appears only after several hours and commonly reaches a maximum level at 24 to 48h, thereafter subsiding (Roitt, 1984).

3. Reaction to Adjuvant

Many inactivated vaccines contain adjuvants that are responsible for potentiating the immune response by creating a depot effect in the tissues to provide a prolonged antigenic stimulus and by activating macrophages (Roitt, 1984). Under the influence of the repository adjuvant, macrophages form granulomas that provide sites for interaction with antibody-forming cells. The nodule formed

as a result of this reaction is seldom apparent and regresses normally within 2 to 6 weeks. Some adjuvants cause considerable tissue injury like adjuvants of *Clostridium perfringens* are highly irritating and frequently produce abscess. It is also seen that adverse reactions produced by the aluminium hydroxide gel vaccine are milder in comparison to those produced by the alum-precipitated vaccine. Oil adjuvant (Freund's type) vaccines cause several granulomatous reactions. Oil adjuvant of *E. coli / Campylobacter* bacterin (vaccine) may cause unilateral to bilateral lameness in bovines (Chauhan, 2018). A similar type of reaction can occur due to other components, such as stabilizers and emulsifiers, in the vaccine.

4. Diluent and Contamination Problems

Unsuitable diluents such as autoclaved tap water, have been reported to cause systemic and local reactions, probably due to these diluents containing pyrogens and/or toxic ions (Revan, 1989). Problems have also been experienced with contamination of lyophilized vaccine through the use of multidose bottles of diluent. Contaminants identified in multidose diluent bottles have included *Pseudomonas* spp. and barbiturates. Such contaminants may cause local or systemic reactions.

5. Administration Technique

Freestone (1979) demonstrated in humans that there can be statistically significant differences in pain and erythema at the injection site recorded by different vaccinators. Marek's disease vaccine is placed s/c in the neck region of day old chicks but when wrong placement of this vaccine is there, it can cause central nervous system problems, twisted neck and even death (Chauhan and Rana, 2010).

Systemic reactions

These reactions can include fever, lethargy, anorexia, oedema, urticaria, vomiting, diarrhoea, corneal opacity, dyspnoea, excitement, collapse, convulsions and, on rare occasions, death. Abdominal discomfort, nausea, vomiting, headache, fever and rash or urticaria is often observed after vaccination with typhoid vaccine (Engels *et al*., 1998). Myalgia, rash, headache, malaise, joint aches, nausea, vomiting and loss of appetite along with chills and fever are reported after anthrax vaccination in humans (CDC, 2010). Peripheral neuropathy, particularly brachial plexus neuritis is observed after hours to weeks of tetanus toxoid administration (Wassalik *et al*., 2008). Febrile seizures are observed within 3 days of DTwP (Diphtheria, Tetanus and whole-cell Pertussis) and Diphtheria, Tetanus and Acellular pertussis (DTaP) vaccination (Cody *et al*., 1981; Farrington *et al*., 1995; Edwards *et al*., 2008). Possible causes are given below:

1. Type I Hypersensitivity - Anaphylaxis

Systemic anaphylaxis is rare but can have dramatic clinical signs, which vary with the species. Clinical signs in dogs include an initial restlessness, vomiting, diarrhea and dyspnoea, while in cats peripheral irritation, pruritus, vomiting and dyspnoea are seen (Trinca, 1979; Tizard 1982). Some cases can progress to collapse and death. In cattle and goats shortly after paratuberculosis vaccination progressive diarrhoea is seen (Chauhan *et al*.,2001).

2. Type III Immune-Complex mediated Hypersensitivity

In these reactions, antigen-antibody complexes lead to the activation of the complement system resulting in the release of histamine and lymphokines, microthrombus formation and inflammation (Trinca,1979). It is possible in young, small puppies with maternal antibody that antigen-antibody complexes activating the complement system and causing the release of lymphokines could be part of the pathogenesis of the lethargy sometimes seen after vaccination. Anxiety, stress and car-sickness could also be involved in some cases. Blue-eye in dogs is a type III hypersensitivity reaction after immunization with living canine adenovirus I or natural infection with this virus. This condition is no longer seen as a complication of adenovirus vaccination due to the use of canine adenovirus 2 in all living infectious canine hepatitis vaccines, rather than canine adenovirus 1. According to Albritton (1996) a number of dogs have been observed to develop conditions which appear to be immune-mediated, following annual vaccination, at an incidence which is greater than that which has been observed in previous year. A controlled epidemiologic study of this possible relationship found that, when compared with a randomly selected hospital control group of dogs, dogs with IMHA (Immune Mediated Hemolytic Anemia) were more likely to have been vaccinated within the previous month ($p < 0.0001$) and the dogs with IMHA that had been vaccinated in the previous month had more severe disease than those with IMHA that had been vaccinated more than 1 month previously (Duval and Giger, 1996). Also cutaneous vasculopathy may follow rabies virus vaccination, where vascular deposition of rabies virus antigen and complement is demonstrated by immunohistochemical studies (Wilcock and Yager, 1986; Vitale *et al*., 1999). *Brucella abortus* strain 19 vaccinations in cattle may produce lameness and chronic granulomatous athropathy in various joints due to deposition of immune complexes. In calves after immunization with *Salmonella typhimurium* vaccine, renal lesions are observed due to deposition of immune complexes (Chauhan, 1998).

3. Autoimmune diseases-

Tissue depots of an aluminium adjuvant have been linked to symptoms of chronic fatigue syndrome in Macrophagic myofasciitis (MMF) (Cherin *et al.*, 1998). Children immunized with European strain of influenza virus containing a squalene emulsion adjuvant show narcolepsy

(Nohynek *et al*., 2012; Partinen *et al.*, 2012). Risk of developing narcolepsy was estimated at 1:16,000 vaccinated Finnish 4- to 19-year-olds (Nohynek *et al.*, 2012).

4. Diluent and Contamination Problems

An unsuitable or contaminated diluent can cause pyrexia and other systemic signs as well as the local reactions.

5. Endotoxins

There have been reports of endotoxins in a *Bordetella bronchiseptica* vaccine causing systemic reactions in dogs of all ages (Rishniw, 1990; Punch 1990). Reactions have included depression, shivering, tremors and severe vomiting.

Pain

Pain due to vaccination can be caused by a number of different components of the vaccine; these can include stabilizers, various salts and formaldehyde. High or low pH and osmotic concentration, or low temperature of the vaccine on administration can all produce pain response. There have been instances when some veterinarians in a practice have observed a painful stinging reaction to a vaccine but other veterinarians in the same practice, using the same batch of vaccine, have not observed the same effect.

Residual Virulence

The classical veterinary example of residual virulence is that of panleukopenia vaccine virus causing cerebellar hypoplasia in newborn kittens. This **i**s rarely seen today because veterinarians and breeders are aware of the dangers of panleukopenia virus to newborn kittens, and now have an inactivated vaccine available that is safe for all ages. However, problems can still occur with living attenuated feline rhinotracheitis and feline calicivirus vaccines, if vaccine **i**s spilled on to the hair coat or is aerosolised during inoculation (Povey, 1980). In these instances cats can show mild signs of infection and possibly increase the virus load in the environment. Thi**s** may be important in a cattery where there are large numbers of susceptible individuals. Attenuated canine parvovirus and canine distemper virus multiply in lymphopoietic tissue and certain strains may possibly cause destruction of lymphopoietic tissue leading to immunosuppression (Phillips *et al.***,** 1989). This could be significant if there is a possibility that a dog is incubating an infectious disease when vaccinated. In this circumstance vaccination is contraindicated as the risks of vaccination may outweigh the possible benefits. Some complaints concerning possible residual virulence arise because the dog is incubating infection, especially parvovirus, at the time of vaccination. OPV (Oral poliovirus vaccine) in humans carries the risk of vaccine-associated paralytic poliomyelitis (VAPP) particularly among infants who receive the vaccine for the first time and their contacts (WHO polio vaccine information sheets). After OPV administration on rare occasions, particularly in immunodeficient infants, aseptic meningitis and encephalitis is observed (Andronikou *et al*., 1998; Yeung *et al*., 1997; Rantala *et al*., 1989).

Failure to Protect

The immune response, being a biological process, never confers absolute protection and is not the same in all members of a vaccinated population. Since the immune response is influenced by a large number of genetic and environmental factors, the range of immune responses in a large, random population of animals tends to follow a normal distribution. This means that, whereas most animals tend to respond to antigens by mounting an average immune response, a small proportion will mount a very poor immune response. This latter group of animals may not be protected against infection in spite of vaccination. Therefore, it is statistically not possible that 100% of a random population of animals will be protected by vaccination (Tizard, 1982; Smith *et al*., 1985). Viral vaccines used in dogs and cats are highly efficacious and stringent investigations into a number of apparent vaccine failures have frequently revealed that animals have either not been vaccinated, have been vaccinated while having maternal antibody, have been incubating the disease before vaccination or are suffering from an unrelated condition presenting with similar symptoms. True vaccine failure can be due to vaccine virus in a living vaccine being killed. Live virus vaccines do not contain enough antigens to immunize the animal, unless the virus can infect and replicate in the host (Schulze, 1982). Incorrect storage, the use of chemicals to sterilize syringes or the use of skin disinfectants can lead to the inactivation of vaccine virus, rendering the vaccine ineffective (Tizard, 1982).The normal immune response can be suppressed by a number of causes. Stress in general, including pregnancy, extremes of cold and heat (Webster,1975), fatigue or malnutrition, can inhibit the normal immune response, probably because of increased steroid production (Tizard, 1982). Protein and vitamin deficiencies have been shown to markedly reduce antibody production after distemper vaccination, and it would appear that such results are analogous to those of the parasitised and malnourished dog (Sheffy, 1966). Antigenic competition following reconstitution of a multi-component canine vaccine has been reported to interfere with the immune response of some dogs (Davies and Pidford, 1991).Therefore, multi-component vaccines and especially combinations of vaccines should only be used when they are known to have been tested for compatibility. Interference with the immune response due to maternal immunity is probably the most important cause of vaccine failure. The recognition that dogs with maternal antibody against canine parvovirus sufficient to inhibit active immune responses to parvovirus vaccine still may be infected with virulent canine parvovirus is of critical importance to the understanding of why many parvovirus immunization failures occurs in young puppies (Carmichael *et al*.,1983).

Despite efficacious vaccines, it should be noted that it maybe impossible to control parvovirus in endemically infected kennels by vaccination alone. McGavin (1989) pointed out that continued attention to both disinfection and vaccination is required to control parvovirus and similar conclusion can be applied to other diseases that spread horizontally. The finding that maternal antibody to canine parvovirus may decline more rapidly than anticipated upon being exposed to virulent endemic parvovirus could crucially affect control programs based on the segregation and isolation of puppies.

CONCLUSION

Vaccine are made in a laboratory setting and its efficacy is tested in controlled environment and the vaccines that had been proven effective during laboratory analysis when sold on a large scale, after encountering field conditions may not show the same features and can even produce complications. In general, clinical trials conducted to evaluate the efficacy of veterinary vaccines prior to their licensing often include less than 100 animals. While this may be sufficient for a manufacturer to demonstrate efficacy and obtain a license, it is unlikely to reveal adverse effects even when the incidence is high. For example, if a disease like immune-mediated hemolytic anemia (IMHA) occurs at a rate of 2 per 10,000 dogs per year independent of vaccination in the general population, and if a new vaccine induces IMHA at a rate of 50 per 10,000 dogs per year, then a clinical trial of approximately 2500 dogs will be needed to have a 90% probability of detecting this adverse effect. If these two rates are lower, for example, 2 per 100,000 dogs and 50 per 100,000 dogs, respectively, then approximately 20,000 dogs will be required. Surely such studies are not feasible or likely to be conducted in the future. So where then will accurate data come from to measure the safety of a vaccine so that any adverse effects can be detected before they occur in near-epidemic proportions following its widespread use? Also though rare but some vaccine related adverse reactions depend on the area or geoclimatic environment of the vaccines so prior precautions should be taken in such cases. Also one in 500 children are born with a problem with their immune systems that could cause serious or life-threatening reactions when vaccinated. A special vaccination strategy should be designed for immunosuppressed and sensitive individuals so as to have larger vaccine coverage with minimum or no adverse effects. Also strict guidelines should be made and followed regarding vaccine preparation and vaccine trials should be supervised properly, and if possible these should also be tested like standard drug which include double blind placebo trials i.e., comparison should be done between vaccinated and unvaccinated individuals and not just between one vaccinated group and other vaccinated group.

For this, we can think of adverse vaccination reactions as a risk and apply the principle of risk assessment which basically include four steps which are usually undertaken to assess risk: (1) hazard identification, the determination of whether a particular substance or procedure is or is not causally linked to a particular health effect; (2) dose response assessment, the determination of the relation between the magnitude of the exposure (e.g., frequency or time since last vaccination) and the probability of occurrence of the health effects in question; (3) exposure assessment, the determination of the extent of exposure; a description of the population at risk; and (4) risk characterization, a description of the nature and the magnitude of risk, including the uncertainty associated with it. This last step can be performed by combining the results of exposure and dose-response assessments. But here risk assessment might stop with the first step i.e., hazard identification, if no adverse effect is found, or if it is decided to take action without further analysis. To be effective as a method of disease control and prevention, post marketing surveillance should be given importance and it should involve four interrelated components, namely, data collection, analysis, interpretation, and timely dissemination. This can be done by increased ascertainment of adverse reactions by encouraging more complete reporting by veterinarians/ medicos. Also vaccine manufacturers should standardize their reporting systems to be consistent with each other in terms of the type and severity of adverse reactions. Criteria should be developed for analyzing and reporting adverse reaction data on a regular basis. This should include establishing statistical methods to determine when an adverse reaction rate exceeds the expected value, which is the fundamental definition of an epidemic. No universal criteria can necessarily be applied to determine the excess number of adverse reactions sufficient to warrant further investigation. The decision to investigate is influenced by many factors such as the severity of the health consequences and the particular circumstances of the events. Also this analysis should exclude reports thought to be invalid, because they are either mis-directional or unreliable.

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