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Accidental Introduction of Viruses into Companion Animals by Commercial Vaccines

James F. Evermann, PhD

Department of Veterinary Clinical Sciences, Washington Animal Disease Diagnostic Laboratory, College of Veterinary Medicine, Washington State University, Pullman, WA 99164, USA

> Nevertheless, we can be confident that all future viruses will arise from those now existent: they will be mutants, recombinants, and reassortments [1].

Vaccination of dogs and cats has been regarded as one of the major success stories in veterinary medicine. Originally, the use of vaccines was to provide a barrier to infectious agents, such as rabies, that were known to be transmitted between dogs and human beings [2]. As public health concerns were addressed, the use of vaccines to control infectious diseases that cause high morbidity or high morality were then included in vaccination programs [3–6]. Vaccination has been proved to be the most efficient and cost-effective method of controlling the major infectious diseases in domestic animals [7,8]. Although we do not normally consider vaccination as way for an animal to become infected with a microorganism, it was originally intended for this purpose—a planned infection with a known infectious dose of nonlethal consequences. Later, vaccines with attenuated (modified) microorganisms that induced a sustained protective immune response with minimal side effects were used [7–10].

The key objective of this article is the recognition of the fact that the use of vaccines is not without risks and what clinicians can do to assist in the recognition and reporting of such adverse events. The main focus is on contamination of vaccines, the types of contaminants, and the effects on vaccinated animals.

PRINCIPLES AND TYPES OF VACCINATION

There are three types of vaccine strategies used in veterinary medicine [11]. These include (1) routine vaccination of susceptible animals to maintain "herd immunity" against endemic or established infections in an area; (2) strategic vaccination that uses emergency vaccination, ring vaccination, and barrier vaccination; and (3) suppressive or dampening-down vaccination. The primary type of vaccination used in companion animals is routine vaccination, because

E-mail address: jfe@vetmed.wsu.edu

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disease prevention in an individual animal is the objective. Forms of strategic vaccination are used in areas that are trying to control infectious diseases in populations, such as in kennels or catteries, however [8]. A further division in vaccines has been the labeling of vaccines based on their clinical importance [4,7]. Essential, or core, vaccines are those vaccines that are recommended to be administered routinely to dogs and cats to protect them against endemic diseases that have high morbidity or mortality rates. Optional, or noncore, vaccines are those vaccines that are not recommended to be used routinely because the disease risk is considered to be lower. It should be emphasized that noncore does not mean nonessential, however, because certain animal populations are at high risk for disease, such as canine coronavirus (CCV) in breeding kennels [12], and canine leptospirosis in outdoor hunting dogs [4].

Vaccines are differentiated into two categories based on whether the immunogen is live or inactivated (killed) [7]. Live vaccines have usually been attenuated by some process to render them avirulent when introduced into an immunocompetent animal. The process can include passage of the virus in cell cultures, temperature selection of mutants, and recombinant technology using vectors [4,7]. Killed vaccines have been inactivated by physical or chemical methods that destroy the infectivity but retain the immunogenicity necessary to induce a protective immune response. The advantages and disadvantages of live and inactivated vaccines are listed in Table 1.

VACCINE REGULATION

Extensive quality control measures have been established over the years to ensure that the vaccines used in human beings and animals are pure, safe, and efficacious [13–17]. Standards for animal vaccines are well outlined, and quality control is highly regulated by the US Department of Agriculture (USDA)–Animal and Plant Health Inspection Service (APHIS) [16]. Despite this scrutiny, there have been occurrences in which adventitious microorganisms, primarily viruses, have been known to enter vaccine production and become part of the vaccine on release (Fig. 1). The ways in which viruses enter into the vaccine production cycle have been reviewed extensively [7,18–23]. They include (1) contamination of the original viral seed stock used to prepare the vaccine, (2) contamination of the cell cultures used in production to amplify the known virus in the vaccine pool, and (3) contamination of the reagents used to propagate the cells being used to amplify the known virus for vaccine production. These are important points to consider and are discussed in further detail.

Contamination of the original viral seed stock would be when a known virus is being selected for eventual use in a vaccine. An example would be using an isolate of feline calicivirus that was derived from a cat with severe clinical symptoms. In the process of isolation, a passenger virus, such as feline panleukopenia, would also be isolated but not detected because of low virus titer or absence of cytopathologic findings. Usually, the virus being selected would be taken through steps to exclude passenger viruses by plaque purification

Table 1
Advantages and disadvantages of live (attenuated) virus and killed (inactivated) virus vaccines

	Advantages	Disadvantages
Live vaccines	Mode of action is most similar to natural infection Multiply in host; induce range of immune responses Duration of immunity is usually long lasting No adverse side effects to foreign protein	Possible reversion to virulence Possible contaminating viruses Inference by other agents and passive antibody Storage problems (heating) Possible production of latency Possible induction of abortion Possible shedding to susceptible cohort Temporary immune suppression up to 2 weeks
Killed vaccines	Quite stable Easy to produce	Require large amounts of antigen or may not contain protective antigens Reactions can develop to foreign proteins or adjuvants Immunity is usually short-lived; multiple boosters are required Do not produce local immunity May not inactivate all the agent Other agents that are resistant to inactivating agent may be present (eg, prions) May induce aberrant disease

Adapted from Tizard IR. The use of vaccines. In: Tizard IR, editor. Veterinary immunology: an introduction. 8th edition. Philadelphia: Saunders; 2008; with permission.

or limited dilution steps. Regulations required for vaccine production mandate seed stock purity, and vaccines must pass rigorous USDA standards referred to a 9 Code of Federal Regulations (9CFR) [16,17,23,24].

Examples of the latter two sources of contamination are more common and have been the most documented [21,22,24]. Contamination of cell cultures directly by latent noncytopathogenic viruses or indirectly by reagents used to propagate the cells in the laboratory involves several viruses (Table 2). Most common have been bovine viral diarrhea virus (BVDV), bovine and porcine parvoviruses, and bovine herpesvirus (BHV) type 4 [21,24]. These viruses are frequently present in fetal bovine serum, calf serum, bovine serum derivatives, and trypsin [21]. Although these viruses may have contaminated early serials of companion animal vaccines, there were no apparent serious clinical effects documented, because these viruses did not replicate in dogs or cats or, if replication did occur, there were no symptoms noted at safety testing. An exception to this may have been the association of BHV-4 with urinary tract disease in cats [25,26].

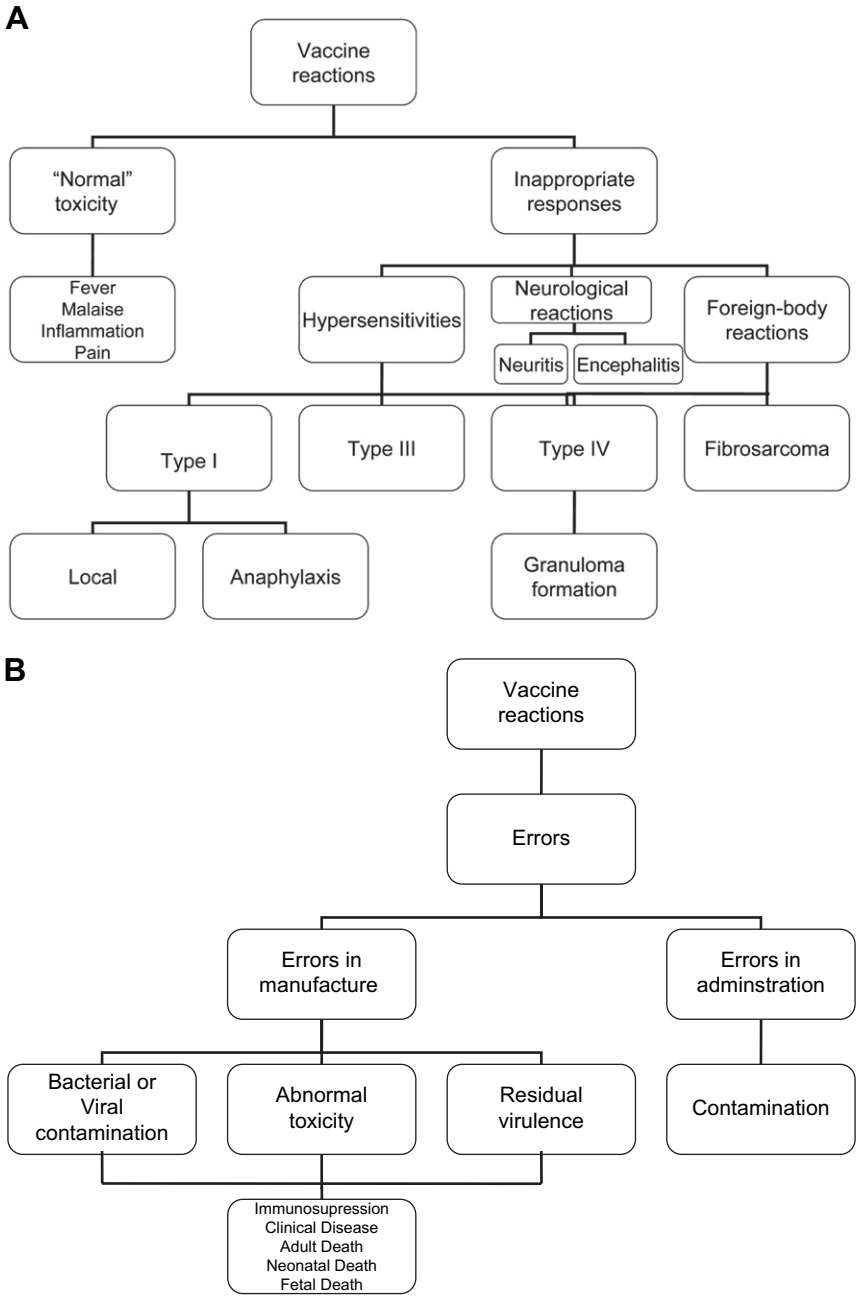

Fig. 1. The major adverse effects of vaccination. (*A*) Vaccine reactions result from normal toxicity and inappropriate responses from the host's immune system. (*B*) Vaccine reactions result from errors in manufacturing and administration. (*Modified from* Tizard IR. The use of vaccines. In: Tizard IR, editor. Veterinary immunology: an introduction. 8th edition. Philadelphia: Saunders; 2008. p. 276; with permission.)

Table 2
Specific viruses that are screened for in bovine serum (calf and fetal origin) and porcine trypsin used in production of veterinary biologics

Bovine serum	Trypsin
Adenovirus (groups 1 and 2)	Porcine adenoviruses
Akabane	African swine fever virus
Bovine coronavirus	Pseudorabies virus
Bovine ephemeral fever	Hemagglutinating encephalomyelitis virus
Bluetongue virus	Bovine viral diarrhea virus
Bovine leukosis	Hog cholera virus
Bovine immunodeficiency virus	Encephalomyocarditis virus
Bovine respiratory syncytial virus	Swine influenza virus
Bovine viral diarrhea virus	Porcine parvovirus
Rift valley fever virus	Porcine respiratory and reproductive syndrome
Vesicular stomatitis virus (Indiana and New Jersey)	Vesicular stomatitis virus (Indiana and New Jersey)
Bovine herpesviruses type 1, 2, 4	Transmissible gastroenteritis
Malignant catarrhal fever	Respiratory variant (coronavirus)
Parainfluenza virus type 3	Porcine enterovirus
Bovine polyomavirus	Vesicular exanthema virus
	Swine vesicular virus

Modified from Merten OW. Virus contamination of cell cultures—a biotechnological view. Cytotechnology 2002;39(2):101; with permission.

NOVEL CONTAMINATE WITH SERIOUS CONSEQUENCES

In 1992, a veterinarian noticed that pregnant dogs were aborting and, in some cases, the dam died as well. A common feature was a history of vaccination 3 to 4 weeks before whelping with a modified-live virus (MLV) multicomponent vaccine [27]. Initially, it was speculated that there was a component of the vaccine, such as canine parvovirus (CPV) type 2 or canine distemper virus (CDV), that was not properly attenuated and that because of the immune-compromised state of the dam, the virus was causing disease. Efforts to isolate CPV-2 and CDV were negative. A virus with properties of an orbivirus was isolated in cell culture from tissue homogenates derived from the diseased pups and dams, however [27,28]. The virus was eventually identified as bluetongue virus (BTV) type 11, a domestic strain of the virus common in the United States [28]. The veterinary biologic manufacturer and the National Veterinary Services Laboratory (NVSL) in Ames, Iowa were informed of the isolation of a potential viral contaminate. In subsequent testing by the NVSL, seed stock virus and repository samples were also found to be contaminated with BTV-11 [29]. The manufacturer voluntarily recalled all vials of the vaccine with serial numbers the same as those associated with the cases.

BTV had not previously been associated with disease in dogs but has been well documented as a pathogen of small and large ruminants [30]. The virus is now known to be present in serum products derived from these ruminants, such as fetal bovine serum. Subsequent studies have demonstrated that canine

cells are capable of being infected with various serotypes of BTV, including BTV-11, without the cell cultures showing any cytopathologic change [31]. The aforementioned reports emphasized the importance of adding BTV detection methods to cells and virus seed stocks being used to produce companion animal vaccines.

ROLE OF VACCINES IN EMERGING VIRUSES

This is a controversial topic and has been debated in the literature over the past several decades [1,32–36]. There are several ways in which the vaccines may contribute to the emergence or re-emergence of viruses in the population. The first is by contaminated vaccines that are used routinely in a large percentage of the animal population. Vaccines that harbor adventitious agents for one species may be pathogenic for another species. Not only may the contaminated vaccine be pathogenic in the vaccinated animal, but it may be spread to other susceptible animals horizontally with the use of aerosols, feces, or saliva, for example (Fig. 2). Documentation of this form of cause and effect with a vaccine and emerging disease would need a thorough case history and laboratory data.

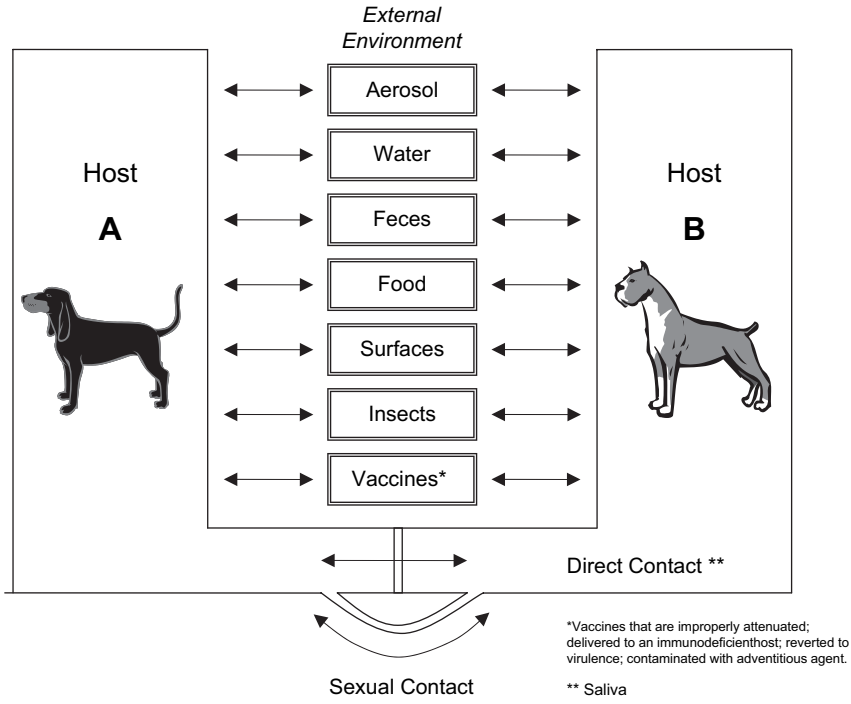

Fig. 2. Pathways of potential horizontal spread of infectious microorganisms. (*Modified from* DeFilippis VR, Villarreal LP. An introduction to the evolutionary ecology of viruses. In: Hurst CJ, editor. Viral ecology. San Diego (CA): Academic Press; 2000. p. 125–208; with permission.)

The second way in which vaccines may contribute to the emergence of new viruses is by immune selection of escape mutants (Fig. 3) [35,36]. Viruses are continually undergoing natural selection because they are obligate intracellular pathogens [37,38]. The immune response is evolving with the emergence of new viruses [39,40]. In some cases, it has been speculated that the use of vaccines causes an enhanced immune selection of viruses that evade the immune response, resulting in sustained infection in the population and disease in a certain percentage of the animals [35,36]. The immune response is a genetically adaptable system to microbial infections [39]. The appearance of new viral infections is most likely manifested first in immunocompromised animals, such as pregnant animals, neonates, and animals that are genetically immune deficient [41].

ENHANCED VIGILANCE: ROLE OF THE CLINICIAN

The emergence or re-emergence of a novel virus occurs in a clinical setting in which (1) well-vaccinated dogs or cats become diseased with clinical signs

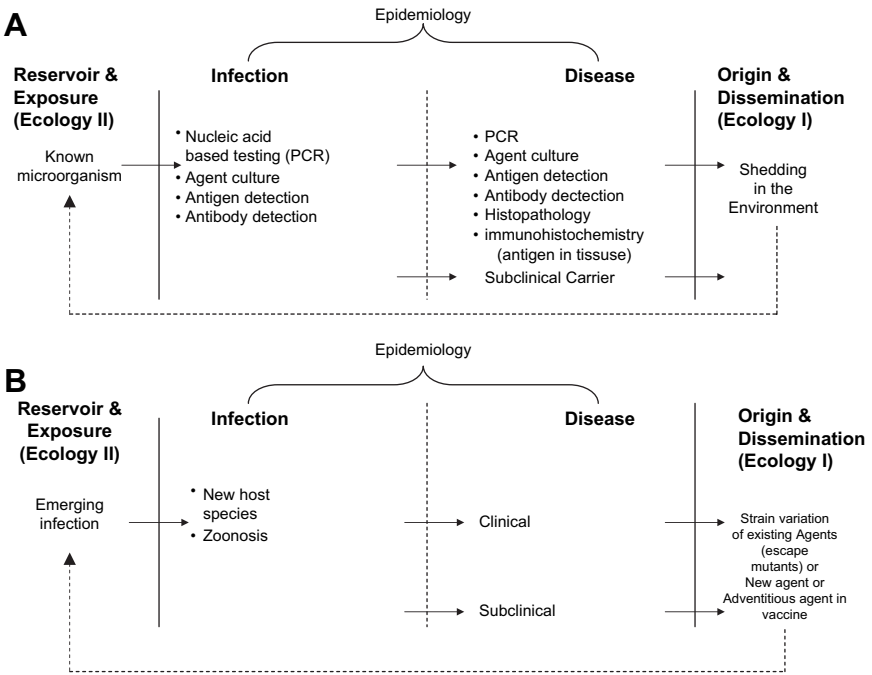

Fig. 3. Schematic of the relations between the epidemiology and ecology of an infectious microorganism. (*A*) Progression of infection to disease or subclinical carrier and the shedding into the environment. (*B*) Origin and dissemination of new microorganisms that emerge by means of mutation, recombination, or an adventitious microorganism in contaminated vaccine. (*Modified from* Evermann JF, Sellon RK, Sykes JE. Laboratory diagnosis of viral and rickettsial infections and epidemiology of infectious disease. In: Greene CE, editor. Infectious diseases of the dog and cat. 3rd edition. Philadelphia: WB Saunders; 2006. p. 8; with permission.)

resembling a virus that the animal should have been protected against by the vaccine, (2) a virus occurs in immunocompromised animals, or (3) a virus is rapidly introduced into a totally immunologically native population of dogs or cats [42]. The diseased animal should be quarantined, and a full diagnostic workup would proceed through a list of differentials [3,42–44]. If a well-vaccinated animal was clinically ill, a diagnostic pursuit would be made in parallel with contacting the biologic manufacturer, and the USDA, Center for Veterinary Biologics [45]. The two-page "Adverse Event Report" can be submitted on-line or faxed to 515-232-7120. This allows biologic manufacturers and the USDA to conduct postlicensure surveillance and to monitor the safety and efficiency of vaccines [9,13,16].

ENHANCED VIGILANCE: LABORATORY LEVEL

Testing for emerging or re-emerging viruses requires a familiarity with the common infectious agents affecting a particular species and maintaining an open mind for unusual observations, such as occurred in the BTV case mentioned previously [27]. The testing for novel viruses would have to be conducted on least at two levels. This would include testing that is done on biologics to ensure their purity before inoculation into animals [20,24] and testing that would be done at the diagnostic laboratory on diseased animals [33,46–49]. Virus-specific detection may involve (1) viral culture in susceptible noncontaminated cell lines, (2) viral antigen detection using immunofluorescence reagents, (3) viral antigen detection using ELISA; or (4) viral nucleic acid detection using polymerase chain reaction (PCR) [19,22,50,51].

DANGER OF CONTAMINATED VACCINES

The danger of a contaminated vaccine may include an immediate effect, such as the clinical effects that were reported after use of the multicomponent canine MLV that was contaminated with BTV [28]. The disease symptoms were confined to the inoculated dogs, and there was no evidence that further spread occurred to other potentially susceptible dogs in the vicinity. In this regard, the scenario would seem similar to the spread of some viruses to a dead-end or accidental host. This has been well documented for insect-borne viruses, such as West Nile virus, in isolated canine cases [48].

The long-term effects of a contaminated vaccine would be more difficult to document, and would require the availability of diagnostic assays specific for the adventitious virus. Because there is a certain degree of natural cross-species infection ("spill over") that occurs in the companion animal population, determining the origin of such an infection would require that the referring veterinarian work closely with the veterinary diagnostic laboratory with case history and sample submission (antemortem and postmortem) [42,52,53]. Once a virus were to spill over to another species, such as a cat to dog with feline calicivirus [46,54,55], the long-term danger is that the virus would establish the dog as a host, with subsequent virus replication, disease, and further shedding to susceptible dogs. This is postulated to have happened when feline

panleukopenia virus crossed species in the late 1970s, resulting in CPV-2 [1,5]. This virus continues to circulate in the canine population, continues to have minor antigenic drifts (CPV-2a→CPV-2b→CPV-2c) [56], and has acquired a dual host range between dogs and cats [33,57].

SUMMARY

The use of biologics in veterinary medicine has been of tremendous value in safeguarding our animal populations from debilitating and oftentimes fatal disease. In parallel to the use of these biologics, there has been the continued evolution of new standards to maintain safety of the vaccines. This article reviewed the principles of vaccination and the extensive quality control efforts that are incorporated into preparing the vaccines. Examples of adverse events that have occurred in the past and how enhanced vigilance at the level of the veterinarian and the veterinary diagnostic laboratory help to curtail these events were discussed. Emphasis on understanding the ecology of viral infections in dogs and cats was introduced, together with the concepts of the potential role of vaccines in interspecies spread of viruses.

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