# Adverse Reactions

After receiving a vaccine(s) intramuscularly, some horses experience local muscular swelling and soreness or transient, self-limiting signs including fever, anorexia and lethargy. Severe reactions at sites of injection can be particularly troublesome, requiring prolonged treatment and convalescence. Systemic adverse reactions (such as urticaria, purpura hemorrhagica colic or anaphylaxis) can also occur. Other systemic adverse reactions have been anecdotally reported.

Veterinarians should report all adverse reactions to the vaccine's manufacturer. Adverse events may also be reported to the USDA Center for Veterinary Biologics at (1-800-752-6255) or through the agency's **web site**.

Vaccine lot and serial numbers should be noted in horses' vaccination records. The ability to provide this information when reporting an adverse reaction will facilitate an investigation.

Adverse reactions are not always predictable and are inherent risks of vaccination. Therefore, it is recommended that horses not be vaccinated in the 2 weeks prior to shows, performance events, sales or domestic shipment. Some veterinarians may elect not to vaccinate horses within 3 weeks of international shipment.

Injection site selection should include consideration of potential adverse reactions. Injection in the gluteal muscles/hip region is not recommended, as gravitational drainage along fascial planes can be obscured. Should an abscess develop, considerable tissue damage can occur and result in eruptions in undesirable locations with lesions that require prolonged time to heal.

The interval from vaccination to scheduled event or a predictable risk of exposure should be sufficient for:

- Generation of a protective immune response to vaccination.
- Recovery from unexpected adverse vaccination reactions that might otherwise interfere with the horse's performance or health prior to, or during shipment.

It should be recognized that:

- Administration of multiple vaccines resulting in administration of both multiple antigens and adjuvants at the same time may increase the risk of adverse reactions.
- Safety and efficacy data are not available regarding the concurrent use of multiple vaccines.
- Administration of MLV and killed vaccines in the same location is discouraged as adjuvants may inactivate the MLV.

Therefore, veterinarians may elect to use a staggered schedule when multiple products are to be administered. Such a schedule should allow at least a 3-4 week interval between inmmunizations.

Vaccines should always be administered by, or under the direct supervision of, a veterinarian, as the possibility of adverse reactions (including anaphylaxis) exists with the administration of any vaccine.

# Special Report

# Summary of adverse event reports for veterinary biologic products received by the USDA from 1999 through 2005

Timothy S. Frana, DVM, PhD; Lawrence A. Elsken, DVM; Steven A. Karli, BS

In the United States, veterinary biologics and veterinary drugs are under the jurisdiction of separate government agencies. Veterinary vaccines and other biologic products are regulated by the USDA,[a] whereas veterinary drugs are regulated by the FDA. The Center for Veterinary Biologics (CVB) is the primary unit within the USDA that implements the provisions of the Virus-Serum-Toxin Act to ensure that veterinary biologic products are pure, safe, potent, and effective.

Although evaluated for safety before licensure, not all potential safety issues can be addressed before a veterinary biologic product is released to the market. Prelicense safety studies may not detect safety concerns because of an insufficient number of animals for low-frequency events, insufficient duration of observation, sensitivities of subpopulations (eg, breed, reproductive status, or use in an unintended species), or concomitant administration of products. Therefore, it is important to gather information on how a product performs under conditions of use.

A system for monitoring problems with veterinary biologic products after licensure was initiated in 1985 and has undergone several changes over the years. The system currently relies primarily on reports from practitioners and consumers; these reports are then entered into an electronic database. The information provided here summarizes adverse event reports received by the CVB from the public, which includes veterinarians, veterinary staff, other health professionals, and animal owners, for the period of 1999 through 2005.

## Procedures for Reporting Adverse Events

An accepted definition of a veterinary adverse event is any observation of an event in an animal or animals, regardless of whether it is considered to be a product-related event, that is unfavorable and unintended and that is detected after use of a veterinary medicinal product. An adverse event report is a direct communication from an identifiable firsthand reporter that includes (at the minimum) the following information: an identifiable reporter, an identifiable animal or animals, an identifiable veterinary medicinal product, and 1 or more adverse events.

From the Center for Veterinary Biologics, USDA–Animal and Plant Health Inspection Service–Veterinary Services, Ames, IA 50010. Address correspondence to Dr. Frana.

Adverse event reports for all veterinary biologic products are submitted to the CVB on a voluntary basis from the public. Adverse event reports may be submitted to the CVB via a toll-free number (800-752-6255), the CVB Web site,[1] mail, or fax. Manufacturers may also submit adverse event reports that they have received; participation of the manufacturers may be voluntary or may be at the request of the CVB. Additionally, adverse event reports related to veterinary biologic products received by the FDA Center for Veterinary Medicine are forwarded to the CVB.

Each adverse event report received by the CVB is reviewed for accuracy and to ensure the information is complete. When additional information is required or deemed important, follow-up contacts are made with the reporter or associated health professional. Adverse events are classified by the reporter, who selects from a list of event categories that includes anaphylaxis-hypersensitivity, autoimmune, birth defect, lack of expected efficacy, local, neoplasia-cancer, reproductive, systemic, or other. Events included in the category "other" included descriptions of neurologic signs, behavior changes, dermatopathies, and various other ailments. Vaccine-associated sarcomas in cats were classified in the neoplasia-cancer category. The report may be reclassified by personnel at the CVB when warranted by analysis of the available information.

On the basis of the seriousness, expectedness, or frequency of the adverse event or events, the CVB may request investigation reports or summary reports from the manufacturer regarding the biologic product or vaccine serial in question. The CVB may also request repeat or additional testing by the manufacturer or the CVB laboratory. Additionally, epidemiologic investigations or additional safety studies may be performed. Although no formal causality assessment is applied to a particular report, each report is reviewed and evaluated by the CVB. If, on the basis of the available evidence, product-related safety or efficacy problems exist, regulatory actions may follow that could include additions or changes to the product label, notifications sent to users, and suspensions of product distribution.

## Adverse Event Reports

The CVB received 5,470 adverse event reports during the period from January 1, 1999, through December 31, 2005. The number of reports for each

year during this time period was calculated (**Figure 1**). These reports included 12,409 affected animals, including 343 reported deaths. Seventeen reports involved ≥ 20 affected animals, which included 2 reports that involved an estimated combined total of 5,600 affected animals. Therefore, those 2 reports accounted for a large proportion of the affected animals. There were 6 reports that had deaths of 10 or more animals, with the highest number being 62 animals that died. For events in which the reporter's relationship to the animal or animals was known, 87% were submitted by veterinarians, veterinary staff, or other health professionals and 12% were submitted by animal owners.

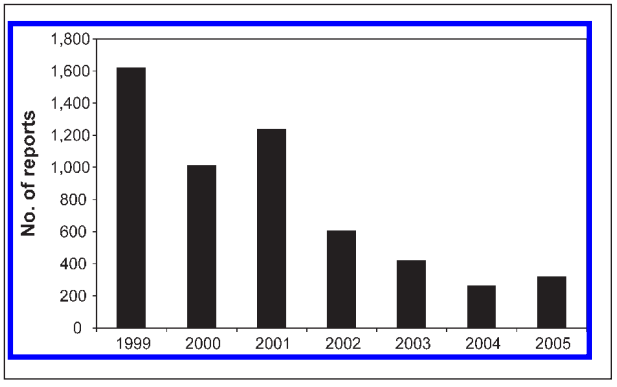


Figure 1—Number of adverse event reports received each year by the USDA Center for Veterinary Biologics (CVB) for the period 1999 through 2005.

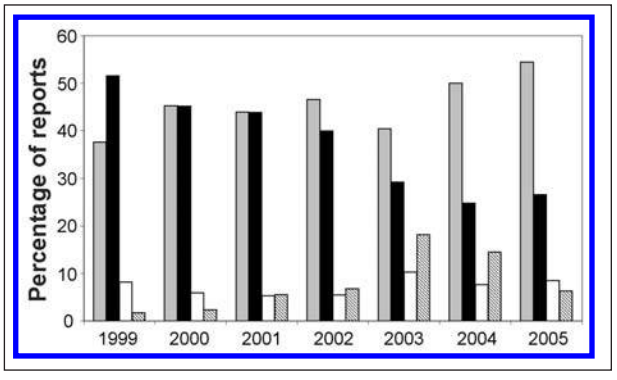


Figure 2—Percentage of total annual adverse event reports for canids (gray bars), felids (black bars), mustelids (white bars), and equids (diagonal-striped bars) received by the USDA CVB for each year of the period 1999 through 2005.

Reported adverse events were categorized as anaphylaxis-hypersensitivity (n = 2,884), local (1,368), systemic (821), other (231), neoplasia-cancer (85), reproductive (41), autoimmune (18), lack of efficacy (13), and birth defect (9). Reports involving canids (n = 2,365) constituted the largest animal group, followed by reports involving felids (2,349), mustelids (ferrets and mink; 382), equids (297), bovids (60), pigs (7), sheep and goats (6), birds (including poultry; 2), and exotic animals (2).

The relative proportion of adverse event reports for canids, felids, mustelids, and equids was calculated for the time period (**Figure 2**). Reports involving canids and felids were nearly equal during the entire period (n = 2,365 [43.24%] and 2,349 [42.94%], respectively). However, since 2002, the number of reports for adverse events in canids has exceeded the number of reports for adverse events in felids. Mustelids, primarily ferrets, were the third most common animal group involved in the reports during this period (n = 382 [6.98%]), and the number of reports for mustelids was fairly uniform during the period, varying from 5.34% to 10.29% on a yearly basis. Reports involving equids accounted for 297 (5.43%) of the total and varied from 1.79% to 18.18% on a yearly basis. Reports involving bovids accounted for 60 (1.10%) of the total and varied from 0.74% to 2.85% on a yearly basis. There were 17 (0.31%) adverse event reports involving pigs, sheep, goats, birds (including poultry), and exotic animals during this period; none of these animal groups had > 3 reports for any given year.

Event categories for each animal group for which there were at least 50 reports were summarized (**Table 1**). In canids, adverse event reports predominantly involved acute anaphylaxis-hypersensitivity reactions (n = 1,564 [66.13%]). In felids, anaphylaxis-hypersensitivity and local reactions were nearly equal (n = 933 [39.72%] and 891 [37.93%], respectively). Mink and ferrets primarily had reports of acute anaphylaxis-hypersensitivity (n = 337 [88.22%]), whereas systemic events were the most

Table 1—Percentage of adverse event reports received by the USDA Center for Veterinary Biologics for the period from 1999 through 2005 for various categories of events and animal groups.*

| Category of adverse event | Canids | Felids | Mustelids | Equids | Bovids† |
|---|---|---|---|---|---|
| Anaphylaxis-hypersensitivity | 66.13 | 39.72 | 88.22 | 10.10 | 26.67 |
| Local | 17.72 | 37.93 | 0.52 | 16.50 | 6.67 |
| Systemic | 11.92 | 15.45 | 8.90 | 37.71 | 41.67 |
| Other‡ | 3.13 | 3.24 | 2.36 | 20.54 | 13.33 |
| Neoplasia-cancer | 0.13 | 3.49§ | 0 | 0 | 0 |
| Autoimmune | 0.72 | 0.04 | 0 | 0 | 0 |
| Reproductive | 0 | 0 | 0 | 11.11 | 10.00 |
| Birth defect | 0 | 0 | 0 | 3.03 | 0 |
| Lack of efficacy | 0.21 | 0.13 | 0 | 1.01 | 1.67 |

*Animal groups represent those for which there were at least 50 reports. †Values in the column do not total to 100% because of rounding. ‡Other includes descriptions of neurologic signs, behavior changes, dermatopathies, and various other ailments. §Vaccine-associated sarcomas in cats were classified in the neoplasia-cancer category.

common reports for equids and bovids (112 [37.71%] and 25 [41.67%], respectively).

## Discussion

The CVB receives adverse event reports for veterinary biologic products from the public, which comprises consumers and veterinarians, veterinary staff, and other health professionals. For the period 1999 to 2005, the annual number of adverse event reports ranged from a high of 1,620 reports to a low of 262 reports. There were substantially more reports received by the CVB in the years 1999 through 2002, compared with the number of reports for the years 2003 through 2005. This is primarily attributable to the fact that the US Pharmacopeia Veterinary Practitioners' Reporting Program ceased its adverse event report program for veterinary medicinal products on April 30, 2003.[2] Since discontinuance of that reporting program, the CVB typically has received 25.6 reports/mo (approx 307 reports in any 12-month period).

In addition, adverse events for veterinary biologic products may have been reported only to the manufacturers of those products. The manufacturers of veterinary biologic products have not been required to routinely furnish reports they receive to the CVB. Thus, the information provided here consists primarily of adverse event reports made directly to the CVB and may not be representative of the number or type of events reported directly to biologics manufacturers.

Since 2002, the percentage of reports involving canids has been greater than the percentage of reports involving felids. The reason for this pattern is not clear because the number of cats in US households is greater than the number of dogs in US households, and the rate of increase in cat ownership has outpaced that for dog ownership.[3] The highest numbers of adverse event reports for equids were in 2003 and 2004 and were primarily related to reports involving reproductive and birth defects after administration of a product that contained West Nile virus. A causal relationship was never established, and a subsequent study[4] provided evidence that the product did not compromise pregnancy in horses.

Anaphylaxis-hypersensitivity reactions were the most numerous type of adverse event reported, comprising 2,884 (52.72%) of the reports received. However, this category of reports varied from 10.10% for equids to 88.22% for mustelids. Two studies[5,6] have revealed the predisposition of ferrets toward anaphylactic reactions. In the study reported here, adverse events for canids were predominantly acute hypersensitivity reactions (66.13%). This is comparable to results for a study[7] in which investigators evaluated adverse events after vaccine administration in dogs. In that study, the predominant clinical signs in a sample of 400 affected dogs were facial or periorbital edema (30.8%), urticaria or wheals (20.8%), and generalized pruritis (15.3%). If these reports had been received by the CVB, they would have been classified as hypersensitivity events.

Adverse event reports for felids were nearly equally divided between anaphylaxis-hypersensitivity and local reactions (39.72% and 37.93%, respectively). There were 82 reports categorized as neoplasia-cancer for felids during this period, which ranged from no reports of this type for 1999 and 2000 to a high of 34 reports of this type in 2003. Nearly all of these events were described as fibrosarcomas or vaccine-associated sarcomas by the reporters.

Adverse event reports for equids were most likely to be classified as systemic (37.71%), which was followed by other (20.54%), local (16.50%), and anaphylaxis-hypersensitivity (10.10%). The 60 adverse events for bovids were classified as systemic (41.67%), anaphylaxis-hypersensitivity (26.67%), other (13.33%), reproductive (10.00%), local (6.67%), and lack of efficacy (1.67%). The classification of adverse event reports for other species groups was not provided here because of the low numbers of reports (ie, < 50 reports/species group) for each.

This summary reflects adverse events reported to the CVB for the period 1999 through 2005. The USDA–Animal and Plant Health Inspection Service is interested in all potential associations between vaccines and adverse events. Reports are evaluated to identify unexpected patterns in the number, type, or seriousness of events, but should not be considered as documentation that a vaccine caused the event. The information reported here highlights the role veterinarians have in postmarketing surveillance of veterinary biologic products and detection of adverse reactions that may not be discernable by other means.

a. Regulatory authority for the USDA is provided under the Virus-Serum-Toxin Act of 1913 as further amended by the 1985 Food Security Act. Title 9 of the Code of Federal Regulations, parts 101 to 123, contains the regulatory requirements and standards for the Virus-Serum-Toxin Act.

## References


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