Commentary

Postmarketing surveillance for dog and cat vaccines: new resources in changing times

George E. Moore, DVM, MS, PhD, DACVPM, DACVIM; Timothy S. Frana, DVM, MPH, PhD, DACVPM; Lynn F. Guptill, DVM, PhD, DACVIM; Michael P. Ward, BVSc, MS, MPVM, PhD; Hugh B. Lewis, BVMS, DACVP; Lawrence T. Glickman, VMD, DrPH

Adverse events associated with vaccines are of particular concern to practitioners, animal owners, and vaccine manufacturers because vaccines are generally administered to healthy animals, following the medical dictum to "first do no harm." Prelicensing safety trials of veterinary vaccines are designed to identify the nature and frequency of potential adverse events, but they are limited by small sample size and short duration of follow-up. In general, sample sizes range from 500 to 1,500 animals from at least three distinct geographic sites with a postvaccination observation period of 10 to 30 days. Specific sample size and observation periods are reviewed by the USDA on a product-by-product basis,[1] but limitations remain, principally because of economic reasons. Adverse events that are relatively uncommon or that occur in high-risk subgroups (eg, elderly animals or specific breeds) are usually only detected through postmarketing surveillance.[2-4] The full safety profile for a given vaccine can only be determined after the vaccine has been licensed and administered to large numbers (often millions) of individuals.[5]

Traditional Regulatory Monitoring

Postmarketing surveillance of veterinary and human vaccines relies primarily on spontaneous and passive reports because of their low cost. In the passive surveillance of companion animal vaccines, the regulatory agency depends on practitioners, pet owners, or vaccine manufacturers to notify them of any suspected adverse events subsequent to vaccine administration. The licensing agency for veterinary biologics in the United States is the USDA **Center for Veterinary Biologics (CVB)**. The CVB's Unit of Inspection and Compliance accepts adverse event reports for all large and small animal vaccines,[6] but practicing veterinarians are not legally required to report those adverse events. In contrast, since 1986, physicians have been federally mandated to report adverse events related to human vaccines to the FDA.[7] Through voluntary reporting, the CVB received 1,200 to 1,600 adverse event reports yearly from 1999 to 2001 and only 400 to 600 reports in 2002 and 2003 for all veterinary biologics. More than 80% of those reports were related to canine or feline vaccines, although they represented < 40% of all veterinary vaccines sold.

Each adverse event report received by the CVB is reviewed for accuracy and completeness. Additional information is obtained if needed through follow-up contacts. On the basis of the type of event or the product involved, the CVB may request repeat or additional testing by the manufacturer or the CVB laboratory. The CVB may also request individual investigation reports or summary reports from the manufacturer regarding a product or vaccine serial lot in question. On the basis of a specific report submission or as part of routine monitoring, reports received by the CVB may be reviewed for unusual adverse event patterns associated with a vaccine or serial lots of vaccine. A causality assessment algorithm is not typically applied to individual reports.

Most veterinarians report adverse events directly to the vaccine manufacturer rather than to the CVB. Routine reporting by manufacturers to the CVB is not required at this time, but manufacturers must provide adverse event information whenever requested by the CVB or during regular unannounced inspections that typically occur every 24 months. Additionally, manufacturers are required to immediately report to the CVB any indications of problems with the purity, safety, potency, or efficacy of a vaccine.[8] Although the term immediately has been interpreted to mean within one working day, specific indications for reporting are not defined by regulation. The current reporting system limits the ability of the CVB to estimate the true frequency and pattern of vaccine-related adverse events and to generate meaningful causal hypotheses.

An additional voluntary reporting program, the **US Pharmacopeia (USP)** Veterinary Practitioners' Reporting Program, was started in 1994 by the USP in cooperation with the AVMA.[9] The USP forwarded each

From the Departments of Veterinary Pathobiology (Moore, Ward, Glickman) and Veterinary Clinical Sciences (Guptill), School of Veterinary Medicine, Purdue University, West Lafayette, IN 47907-2027; the Center for Veterinary Biologics, USDA-Animal and Plant Health Inspection Service-Veterinary Services, Ames, IA 50010 (Frana); and Banfield, The Pet Hospital, 11815 NE Glenn Widing Dr, Portland, OR 97220 (Lewis). Dr. Ward's present address is the Department of Veterinary Integrative Biosciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX 77843-4458.
Address correspondence to Dr. Moore.

vaccine-related report from veterinarians or owners to the manufacturer, the USDA CVB, and the AVMA. However, the USP discontinued this program in April 2003.[10]

Industry Postlicensure Monitoring

Like the CVB, vaccine manufacturers rely on veterinarians and owners to voluntarily report adverse events associated with vaccine administration. It has been estimated that more than 90% of veterinarians report vaccine-related problems directly to the manufacturer rather than to the CVB.[3] Such information is usually submitted by telephone to the manufacturer's professional or technical services section, and it is subsequently retained by the company. The potential for regulatory license restriction or revocation may serve as a disincentive for voluntary reporting by companies to the CVB, particularly if other manufacturers are not similarly reporting information about their products.

Although the CVB cannot define the population of pets receiving a given vaccine, manufacturers may estimate reporting rates on the basis of sales information (eg, number of vaccine doses sold per unit of time). Manufacturers also can compare the frequency and pattern of adverse event reports with historical data, but such estimates of adverse event rates are typically not released to veterinarians, the public, or the CVB. The CVB has proposed mandatory routine reporting by industry of adverse events related to veterinary biologics, and the draft regulation is in review.[11]

Strengths and Limitations of Passive Reporting of Vaccine-associated Adverse Events

A major advantage of spontaneous reporting systems, in addition to their cost-effectiveness, is the breadth of surveillance in terms of the population number, species, age, breed, sex, geographic dispersion, and variety of vaccines. Rare or serious adverse events that were not identified during prelicensure field trials may be detected through postmarketing surveillance. The purpose of passive systems is mainly to give alarm signals.[12] Hypotheses can then be generated about causality in specific high-risk population subgroups and tested in subsequent investigations or epidemiologic studies. Practitioner-initiated reports to the CVB concerning abortion and death in bitches within 10 days of vaccination led to a CVB investigation and laboratory identification of bluetongue virus as a contaminant in serial lots of a multivalent canine vaccine.[13]

Spontaneous reporting or passive surveillance systems have inherent limitations that would remain even if reporting by veterinarians was mandated. The lack of formal case definitions for vaccine-associated adverse events creates variability in reporting standards, and submissions are primarily nonstandardized descriptions of signs temporally associated with vaccination.[14] To promote sensitivity over specificity, proof or strong evidence of causality between the adverse event and vaccine is not required prior to submitting a report. This allows for report submission of events perhaps previously unassociated with a particular vaccine, but although such reporting reduces the number of false-negative events, the number of false-positive events is increased.

The type and number of adverse event reports may also be influenced by reporter biases and the level of suspicion of an association between an event and vaccination. Health care professionals and owners probably vary in their individual inclination to submit a report, and both may be influenced by media reports.[15] Additionally, the rate of adverse event reporting is known to vary over time, with the highest rates occurring soon after a product is first marketed.[16]

Epidemiologic Follow-up Investigations

The potential for misinterpretation of spontaneously reported adverse event data is great.[2] Perhaps the greatest shortcoming occurs when an attempt is made to draw conclusions from reports alone (numerator), without regard to the exposed (ie, vaccinated) population (denominator) or without comparison to a similar or control group.

Epidemiologic studies generally seek information from population groups for all four cells of a 2 × 2 table (eg, vaccinated [yes or no] and adverse event [yes or no]; **Figure 1**). The rates at which adverse events occur in the groups of interest can be compared statistically to determine the likelihood that differences in these proportions would have occurred by chance alone. Adverse event reports only provide information for one of the four cells (cell a in Figure 1), and even this information may be incomplete or biased. Epidemiologists also seek to identify vaccinated animals that have not had an adverse event because such animals constitute most of the vaccinated (exposed) population. The two other cells of the 2 × 2 table are formed by the control or comparison group and theoretically consist of all unvaccinated animals. Because medical information from large numbers of unvaccinated pets is very difficult to obtain, other vaccinated pets can serve as a comparison group for assessment of relative risk or odds ratios for potential risk factors such as age, weight, breed, or different vaccine types.

Even when population information is available and a significant increase in adverse event risk has

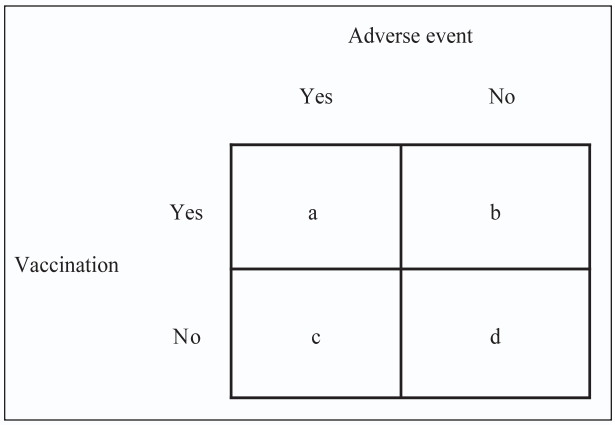

Figure 1—Illustration of a 2 X 2 table used for comparison of potential adverse event cases (a + c) and noncases (b + d) in relation to exposure (ie, vaccination; a + b) or absence of exposure (c + d) in a population. Data for all four cells are required for calculation of relative risk or odds ratio.

been detected statistically, causality is still not proven. Assessment of causality is difficult, and several features provide important evidence that an association is causal, including the temporal relationship, strength of the association, dose-response relationship, and biological plausibility.[17] Causality may never be conclusively determined for some low-frequency or rare events because of the very high cost of controlled clinical trials of appropriate size. Nevertheless, proper epidemiologic investigations allow regulatory agencies to make informed decisions that may reduce the risk of adverse events.

Use of Veterinary Practice Databases for Postmarketing Surveillance

The ability to collect medical data from large populations has been hindered in the past by the laborious reading and transfer of information from paper records into analyzable computer-ready data sets. However, the use of large private or corporate computerized veterinary practice databases can enhance surveillance for vaccine-associated adverse events.[18] Although most practices presently lack the automation or population size necessary to adequately support surveillance, large practices increasingly use a common electronic medical record system at multiple locations and store electronic records centrally for improved efficiency and management. For surveillance and epidemiologic investigations, the database should link a specific pet with medical information from a specific office visit. Pet information should include a unique identification number and demographic information, including species, breed, sex, neuter status, dates of birth and death, and owner address. Medical information should include physical examination findings, laboratory and radiographic test results, diagnoses, procedures, and type and quantity of treatments administered; the corresponding dates for each entry should also be included to enable investigators to follow case management over time. Free-text entry of medical notes may be used, but such entries often include nonstandard abbreviations, and the context of an entry may not be interpretable through simple word searches. Pull-down menus with standardized nomenclature and coding should be used as much as possible because they reduce entry variability and spelling errors. Practices may also have established protocols that promote consistency in diagnosis and treatment for certain types of cases. The large size and standardization of automated practice databases can therefore facilitate spatial and temporal surveillance of specific diseases and medical conditions.

Databases generated during the delivery of health care services do not typically require completion of a drug- or vaccine-associated adverse event reporting form. This means that medical information (eg, clinical signs or diagnoses) related to an adverse event is captured automatically and becomes an integral part of the database, thus reducing the problem of underreporting. Because data exist for the complete hospital population, detection of infrequent adverse events on the basis of a specific set of clinical signs or diagnoses (syndromes) can be accomplished by comparing the exposed and nonexposed groups. Estimates of adverse event incidence can also be calculated because the data provide reliable numerators and denominators. Large databases permit several types of rigorous epidemiologic studies, such as retrospective cohort, case-control, and case-crossover studies, which are well suited to vaccine or drug safety investigations.[19,20] Such databases can be so large, however, that it is possible to confuse statistical with clinical significance when an association is made between adverse events and a vaccine or drug.[21] Statistical power in very large populations often produces significant results even when the differences are too small to be clinically important.

Although practice databases may contain thousands or millions of electronic records, the practice's patient population, coding system, and medical information will likely have some limitations. Any given health care organization may be limited in the variety of vaccines or drugs used. Generalizations based on statistical analyses may therefore be constrained if patient demographics, diagnostic procedures, or products used in the practice are not representative of other populations of interest. Large practice databases thus have strengths and limitations, but some of these are complementary to those of spontaneous reporting systems.[22]

Conclusion

In the context of product safety surveillance for human pharmaceuticals, it was suggested that "you can have any two of speed, high quality, and low cost, but you cannot have all three."[16] Public and professional expectations demand the first two; yet, resource limitations will require the third. In seeking to reach these goals, veterinary practice databases can be analyzed to complement spontaneous reporting systems for vaccine safety. Leveraging information technology to improve the power of epidemiologic investigations can increase our understanding of vaccine-associated adverse events in times of increased public consciousness, professional concern, and federal agency resource constraints.

References

1. Animal and Plant Health Inspection Service. Veterinary Services Memorandum No. 800.204. USDA, May 28, 2002.
2. Siev D. An introduction to analytical methods for the postmarketing surveillance of veterinary vaccines. *Adv Vet Med* 1999; 41:749–774.
3. Meyer EK. Vaccine-associated adverse events. *Vet Clin North Am Small Anim Pract* 2001;31:493–514.
4. Chen RT. Special methodological issues in pharmacoepidemiology studies of vaccine safety. In: Strom BL, ed. *Pharmacoepidemiology*. 3rd ed. West Sussex, England: John Wiley & Sons, 2000;707–732.
5. Salmon DA, Moulton LH, Halsey NA. Enhancing public confidence in vaccines through independent oversight of postlicensure vaccine safety. *Am J Public Health* 2004;94:947–950.
6. USDA Center for Veterinary Biologics. Adverse event reporting. Available at: www.aphis.usda.gov/vs/cvb/ic/adverseeventreport.htm. Accessed Jan 5, 2005.
7. Chen RT, Rastogi SC, Mullen JR, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994;12:542–550.
8. Title 9 Code of Federal Regulations, part 116.5. US Government Printing Office, Jan 1, 2004.
9. Meyer EK, Becker SC. The United States Pharmacopeia Veterinary Practitioners' Reporting Program. *J Am Vet Med Assoc* 1996;208:361–363.
10. U.S. Pharmacopeia to close Veterinary Practitioners' Reporting Program. *J Am Vet Med Assoc* 2003;222:1326.

11. United States Government. Proposed rules: 9 CFR parts 101 and 116. *Fed Regist* 2002;67:1910–1913.
12. Miller E, Waight P, Farrington P. Safety assessment post-licensure. *Dev Biol Stand* 1998;95:235–243.
13. Wilbur LA, Evermann JF, Levings RL, et al. Abortion and death in pregnant bitches associated with a canine vaccine contaminated with bluetongue virus. *J Am Vet Med Assoc* 1994;204:1762–1765.
14. Varricchio F, Iskander J, Destefano F, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J* 2004;23:287–294.
15. Wallenstein EJ, Fife D. Temporal patterns of NSAID spontaneous adverse event reports: the Weber effect revisited. *Drug Saf* 2001;24:233–237.
16. Evans SJ. Pharmacovigilance: a science or fielding emergencies? *Stat Med* 2000;19:3199–3209.
17. Fletcher RH, Fletcher SW, Wagner EH. *Clinical epidemiology: the essentials*. 3rd ed. Baltimore: The Williams & Wilkins Co, 1996.
18. Glickman LT. Weighing the risks and benefits of vaccination. *Adv Vet Med* 1999;41:701–713.
19. Moore GE, Glickman NW, Ward MP, et al. Incidence of and risk factors for adverse events associated with distemper and rabies vaccine administration in ferrets. *J Am Vet Med Assoc* 2005;226:909–912.
20. Moore GE, Guptill LF, Ward MP, et al. Adverse events diagnosed within three days of vaccine administration in dogs. *J Am Vet Med Assoc* 2005;227:1102–1108.
21. Strom BL, Carson JL. Use of automated databases for pharmacoepidemiology research. *Epidemiol Rev* 1990;12:87–107.
22. Ellenberg SS, Braun MM. Monitoring the safety of vaccines: assessing the risks. *Drug Saf* 2002;25:145–152.