

# Human Illness Associated with Use of Veterinary Vaccines

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**Veterinary vaccines are being used with increasing frequency in the United States to protect the health of animals. However, humans may be inadvertently exposed to these products by means of unintentional inoculation or other routes of exposure. The potential for both exposure and for adverse consequences secondary to exposure to veterinary vaccines may be growing. With the exception of brucellosis vaccines, there have been few reports of suspected or confirmed adverse events in humans associated with the use of animal vaccines, but it is unclear whether that is because few adverse events occur or because adverse events are not recognized and/or reported. Results of a search for relevant literature and of communications with health officials at governmental and private institutions suggest that enhanced efforts are needed to recognize and to prevent human illness associated with use of veterinary vaccines.**

Veterinary vaccines are being used with increasing frequency in the United States to protect the health of animals. In addition to their direct benefit to animals, these vaccines have also markedly decreased the risk of transmission of many zoonotic infections (e.g., rabies and brucellosis) to humans. The US Department of Agriculture currently licenses >2000 vaccines for use in animals [1]. Most of these vaccines are inactivated formulations, but >500 live vaccine formulations for animals are also licensed. Veterinary vaccines are intended only for use in animals and are not tested for safety in humans. However, humans may inadvertently be exposed to these products by means of unintentional inoculation or other routes of exposure.

The extent to which veterinary vaccines pose a health hazard to humans is unclear. The increased use of veterinary vaccines may be accompanied by an increase in human exposure to the vaccine strains, thus increasing the potential for adverse effects. In addition, new methods of vaccine administration may result in an increased likelihood of inadvertent exposure. For example, increased use of aerosol administration may result in greater human exposure to animal vaccines. For some animal

vaccines, such as those administered to prevent “kennel cough” in dogs, aerosol administration is becoming the preferred route. Also, oral administration of vaccines that contain live agents is becoming more common. Orally administered vaccines have been developed for rabies prophylaxis in wildlife, and millions of baits have been distributed. The administration of live vaccines to animals destined for the human food supply may result in human exposure to a vaccine strain. Illness subsequent to such an exposure is unlikely to be recognized by the patient or the physician as a potential consequence of an animal vaccine exposure.

In addition to an increased risk of exposure, there may be an increased likelihood of an adverse side effect in exposed individuals, because an increasing proportion of the US population is immunosuppressed due to advanced age or other reasons (e.g., HIV infection, receipt of chemotherapy, or receipt of an organ transplant). These populations are known to be at increased risk of zoonotic infection [2], and the likelihood of adverse consequences following exposure to a live animal vaccine or to an animal infected with a vaccine strain is higher for this population than for those who are immunocompetent. Currently, veterinary facilities do not routinely warn pet owners when they are administering live aerosol vaccines in close proximity to the owners, and the risk among immunocompromised pet owners of acquiring an infection with a vaccine strain directly from the vaccine or from shedding of the vaccine strain is unknown.

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There have been few reports of suspected or confirmed problems in humans that are associated with animal vaccines, with the exception of brucellosis vaccines, but it is unclear whether this is because few adverse events occur or because adverse events are not recognized and/or not reported. There is no agency clearly responsible for monitoring and disseminating information on adverse effects in humans that is associated with the use of animal vaccines. Surveillance has not been routinely performed at the national level for adverse human reactions associated with use of animal vaccines.

To ascertain what was known about human illness associated with exposure to animal vaccines, an Internet search for relevant literature was conducted with multiple terms, general terms, such as "veterinary vaccines" and "occupational injury," and disease-specific terms. In addition, health officials at the Centers for Disease Control and Prevention (CDC; Atlanta, GA), the US Food and Drug Administration (FDA), and the US Department of Agriculture (USDA) were contacted, as were a number of professionals at universities, including veterinary schools.

## BRUCELLOSIS

Brucellosis is a zoonotic disease that causes systemic symptoms, including fever of variable frequency and duration, chills, headache, weakness, weight loss, arthralgia, and generalized pain [3]. Brucellosis may persist for days to years, if not treated properly. A notifiable condition in the United States, brucellosis was reported in 87 individuals in 2000 [4].

The causative agent of brucellosis is a small gram-negative coccobacillus of the genus *Brucella* that can infect cattle, sheep, goats, pigs, and dogs. Infection may result in severe illness and death, and the disease remains a significant threat in many developing areas of the world. Humans may become infected, usually because of contact with animals that are infected or with animal products that are contaminated with these bacteria.

The US Brucellosis Eradication Program (Web site, <http://cofcs66.aphis.usda.gov/bad/refbook2000/Brucellosis.pdf>) was established in 1934 as a state and federal partnership with the aim of eliminating brucellosis in cattle, and the program has had considerable success. Human disease, however, has been associated with use of the S19 vaccine, a live bacterial vaccine administered for many years to cattle to control the spread of brucellosis. The current vaccine in use, RB51, is a modified live culture vaccine that was developed and marketed in 1996 as a replacement for the S19 vaccine. License restrictions have limited its use to veterinarians or to those supervised by veterinarians, and distribution has been limited to recipients authorized by state officials. RB51 has been considered less virulent than the S19 strain, on the basis of results of animal testing. However, both local and systemic side effects in humans

have been documented as being associated with the RB51 vaccine.

To assess the risk of disease following occupational exposure to the RB51 vaccine, the CDC initiated a passive surveillance registry in 1998 to report unintentional autoinoculation of RB51 vaccine by veterinarians and by others at risk for occupational exposure (David Ashford, CDC, unpublished data). Twenty-six individuals reported exposure to the RB51 vaccine to the CDC from January 1998 through December 1999. Twenty-one (81%) of the individuals reported needlestick injuries, and, of 5 patients (19%) who were splashed with the RB51 vaccine, 4 were splashed in their conjunctiva and 1 was splashed in an open wound. Even though most individuals (69%) reported receiving prophylactic antibiotics, 19 (73%) reported at least 1 systemic symptom, with 7 (27%) having persistent symptoms for >6 months. One patient required surgery, and *Brucella abortus* strain RB51 was isolated from the patient's surgical wound.

Approximately 4–5 million doses of *Brucella* vaccines were administered annually from 1997 through 2000, and it is estimated that at least 8000 needlestick injuries resulting in unintentional inoculation would be expected during this period (David Ashford, unpublished data). Thus, the number of individuals infected with the RB51 strain may be considerably higher than the number reported to the passive surveillance registry at the CDC. In addition, surveillance is complicated because routine serological tests for the detection of *Brucella* species do not detect exposure to the RB51 strain [5].

There have been reports from other countries of brucellosis following vaccination with a live bacterial strain. Acute brucellosis due to unintentional injection of animal vaccine that contained an attenuated *Brucella melitensis* strain was described in a young veterinarian [6], and 2 cases of brucellosis were reported from Spain [7]. In addition, a 10-year-old boy in South Africa was hospitalized with bacteremia due to *Brucella* after "playing" with vials of brucellosis vaccine on a farm tractor; the *Brucella* species was characterized in the laboratory as the "vaccine strain" (Keith Klugman, Emory University, personal communication).

In addition to direct exposure to the vaccine, *Brucella* infection with RB51 vaccine strain in a stillborn calf has resulted in occupational exposure of at least 9 persons to the RB51 strain; 8 of the 9 individuals began receiving chemoprophylaxis with doxycycline within 1 week after exposure, and none became symptomatic during the 6-month follow-up period [5]. The 14-month-old heifer that delivered the calf was not known to be pregnant when she was vaccinated with RB51 at ~8 months of age, which was within the specified age range for vaccination.

It was recently documented in Israel that the *B. melitensis* vaccine strain Rev.1 could persist in animals and could be se-

creted in milk. Furthermore, they documented an isolate recovered from a human that resembled the vaccine strain Rev.1, on the basis of results of conventional bacteriological testing [8].

The problem of brucellosis in the United States is decreasing as a result of the implementation of the brucellosis eradication program. Although the number of cases may be decreasing, the continued presence of the disease in some areas of the United States, the continued use of the vaccine, and the potential use of *Brucella* species as an agent of bioterrorism make it important that physicians understand the signs and symptoms of the disease, as well as the circumstances under which infection may be acquired. Diagnostic tests for detecting infection with the RB51 strain need to be available. The CDC no longer conducts a formal surveillance registry; however, the CDC continues to provide consultation on brucellosis and to receive reports of prophylaxis failure (telephone number, 404-639-3158); the Center for Veterinary Biologics, USDA, also accepts reports to its Inspection and Compliance Unit.

## **VACCINIA INFECTION ASSOCIATED WITH USE OF ORAL RABIES WILDLIFE VACCINE**

To control the spread of rabies in wildlife populations, live-virus vaccines containing either modified live rabies virus or recombinant vaccinia-rabies glycoprotein virus are placed in oral baits that are then widely distributed in parts of North America and Europe; the recombinant vaccinia-rabies glycoprotein virus is used in baits in the United States. The use of such baits continues to increase, and, until 2000, no adverse events in humans were reported as having been due to human exposure to the vaccine-containing baits. More than 3 million baits had been distributed in Ohio since the beginning of 1997, with >22 million baits distributed nationwide from 1990 through 2000. In Ohio, toll-free numbers are printed on baits, and callers can report baits if they are found. In 20 of 160 reports of contact with a bait, persons reported exposure to the vaccine, with evidence that the inner sachet containing the vaccine had ruptured. Two of the 20 instances of exposure likely involved persons with a contraindication to vaccination with the vaccinia virus. In 1 of these 2 instances, a 26-year-old woman was exposed to the recombinant vaccinia-rabies glycoprotein virus vaccine, which led to severe illness and resulted in hospitalization [9]. The woman was 15 weeks pregnant and had epidermolytic hyperkeratosis. She recovered and later delivered a healthy infant who had no evidence of infection.

The case of vaccinia virus infection in this woman highlights the risk associated with vaccines that contain vaccinia virus, including animal vaccines. A tremendous amount of attention has recently been given to potential adverse events associated with vaccinia vaccine for the protection of individuals against

smallpox. The risk of contact transmission of vaccinia virus via smallpox vaccination has been estimated to be 2–6 cases per 100,000 primary vaccinations, with 1 to 2 cases of eczema vaccinatum resulting from such transmission per 100,000 primary vaccinations [10]. Relatively little attention, however, has been paid to the increasing rate of exposure of humans to vaccinia virus due to contact with wildlife baits. The vaccinia virus strain used in wildlife vaccine may be less virulent than the strain used in the smallpox vaccine currently licensed for human use in the United States. There was only 1 reported case of vaccinia virus infection among 160 reports of human contact with  $\geq 1$  of the 3.8 million baits dropped in Ohio; however, a marked increase in the use of baits may result in more cases of human vaccinia virus infection, including eczema vaccinatum. Physicians should be alert to this possibility when they see a patient with vesicular lesions. Patients with vesicular lesions of unknown etiology should be questioned regarding contact with animal baits. Also, baits should be clearly labeled, such that an exposure of an individual to a bait will be recognized as such and recalled during questioning. The recent change in wrapping the baits to make them blend in with the environment should be assessed to determine whether individuals would recognize bait exposure.

A different consideration is whether the release of live vaccinia virus into the environment may lead to the creation of a wildlife reservoir in the United States for vaccinia virus. Such baits have been used in Europe for 20 years and in the United States for 10 years, and there has been no evidence that vaccinia virus is persisting in the environment. However, Damaso et al. [11] recently reported a viral infection in Brazil that may be the first case of long-term persistence of vaccinia virus in nature in the New World. Virus was isolated from specimens of skin lesions on dairy cows and milkers in Brazil, and sequences of the hemagglutinin gene substantiated the isolate classification as being an Old World orthopoxvirus. The virus was designated the Cantagolo virus (CTGV), and comparison of the hemagglutinin gene sequences with those of the Brazilian smallpox vaccine strain (W-IOC) used >20 years ago and those of CTGV showed 98.2% identity and suggested that CTGV may have derived from W-IOC by persisting in an indigenous animal and now emerging in cattle and milkers as CTGV. Currently, the only known vaccinia virus species established in nature is buffalopox virus, which causes localized lesions on milking buffalo and dairy cattle and causes oropharyngeal lesions in humans who have consumed contaminated unpasteurized milk. Buffalopox virus epidemics were first noted during the smallpox vaccination era in India, Egypt, and Indonesia. The reservoir for vaccinia virus, if it exists, is unknown [12]; it may be indigenous animals (e.g., voles and field mice). Additional follow-up to identify whether rodents or other indigenous animals are carrying the strain and to identify the extent of human disease

would be useful and would assist in the assessment of the potential threat associated with extensive use of wildlife baits for the oral administration of rabies vaccine.

## **BORDETELLA BRONCHISEPTICA**

*B. bronchiseptica* causes tracheobronchitis in dogs and atrophic rhinitis in swine; it also causes disease in rabbits and other mammals. *B. bronchiseptica* infection in humans is considered rare but has been documented in both healthy and immunosuppressed individuals [13–16]. In healthy individuals, pertussis-like illness and chronic respiratory infection have been reported. Some cases of pertussis-like illness in humans have followed exposure to sick pets or farm animals. The disease is more likely to be severe in individuals who are immunocompromised, such as those with Hodgkin disease, cystic fibrosis, or HIV infection [17, 18]. Pneumonia, sepsis, and death have been reported after infection [14,19, 20].

*Bordetella pertussis*, *Bordetella parapertussis*, and *B. bronchiseptica* are closely related species that all may cause respiratory tract infection in humans and other mammals and may express many similar virulence factors [21]. Variant strains of *Bordetella* species exist, and these species are not always distinct [13]. Recent investigations indicate that the species are extremely versatile and can adapt to the environment in a number of host organisms and that host range adaptation appears to be an ongoing process. *B. pertussis* and *B. parapertussis* may have recently evolved from *B. bronchiseptica*, and human pathogens may continue to evolve from *B. bronchiseptica* [15].

*B. bronchiseptica* has a gene that codes for pertussis toxin (PT). Although some experts believe the gene is “silent,” there is evidence that the gene may be expressed in vivo, even though the strains do not produce PT in vitro [18]. Clinical isolates of *B. bronchiseptica* were obtained from 2 immunocompetent children with pertussis-like illness and both were documented to possess anti-PT antibodies, even though the same strains did not produce PT under laboratory conditions [13]. In addition, nosocomial transmission has been documented [22].

There is a previously unpublished report of a child who was exposed to a live *Bordetella* vaccine and developed pertussis-like illness. In October 2000, 5 days after being sprayed directly in the face with a “kennel cough” vaccine, a 14-year-old boy became ill with a pertussis-like illness. His illness was characterized by a paroxysmal cough that persisted for 3–4 months, accompanied by posttussive vomiting. The boy was treated with antibiotics for a suspected case of pertussis; no cultures were performed. No cases of pertussis had been reported in the state during the previous 2 months; no pertussis-like illness had occurred at the boy’s school or on his sports team. He had not traveled the month before the onset of illness, and he was otherwise healthy.

In this instance, a veterinarian had sprayed the 14-year-old boy directly in the face with an aerosol that contained parainfluenza virus and *B. bronchiseptica* live vaccine, known by most pet owners as the “kennel cough” vaccine. The veterinarian had planned to administer the vaccine intranasally to the boy’s dog. The boy was holding the dog’s head; when the dog moved, the veterinarian sprayed the vaccine directly into the boy’s face, and the boy received the dose intended for the 30-kg dog. The veterinarian said “not to worry” and joked that the boy was “now vaccinated against kennel cough.”

In January 2001, the CDC obtained vaccine from the same lot to which the boy was exposed; the vaccine grew 2 morphologically different colonies of *B. bronchiseptica* (G. Sanden, CDC, unpublished data). The USDA processed the licensure of the vaccine, but information on the original safety studies or on recent changes in licensure was not easily accessible (David Dusek, Center for Veterinary Biologics, USDA, personal communication; Notice 00-14, Center for Veterinary Biologics, USDA, <http://www.aphis.usda.gov/vs/cvb/notices.htm>).

It is unknown whether the case of pertussis-like illness in the 14-year-old boy described above was caused by *B. bronchiseptica*. That the exposure occurred was clear, and the duration between exposure and the onset of illness was consistent with such an illness. The fact that no other cases of pertussis-like illness were reported at the boy’s school and in the community at large lends additional credence to the possibility that the illness resulted from exposure at the veterinary clinic.

With the advent of aerosol vaccination in veterinary clinics for companion animals, human exposure to *B. bronchiseptica* has likely increased in recent years. Physicians should ask patients presenting with pertussis-like illness whether they have visited a veterinary clinic or have been exposed to a sick or recently vaccinated animal during the week before the onset of symptoms. If the potential for exposure to *B. bronchiseptica* is present, performance of cultures should be considered before antibiotics are administered.

No special precautions to avoid human exposure are routinely taken during administration of this aerosol animal vaccine. The package insert [23] for the vaccine to which the 14-year-old boy was exposed states that it should be administered via syringe intranasally. Even when administered properly, there may be opportunity for human exposure, especially if the animal sneezes, which is a common occurrence after intranasal administration of a liquid. In addition, the animal may be able to transmit the vaccine strain during the period of active infection.

## **OCCUPATIONAL EXPOSURE TO VACCINES**

Veterinarians are at highest risk of exposure to veterinary biologic products. Occupational needlestick transmission of in-

fectious agents is a significant concern. Although there is no routine reporting of occupational exposures in veterinary settings, some studies have been conducted to examine the rate of needlestick exposure to biologic products. A survey of all women who graduated from US veterinary schools from 1970 through 1980 was conducted; of 2532 respondents, 1620 reported a total of 2663 needlestick events. The reported overall needlestick injury rate was 9.3 sticks per 100 person-years of practice. Substances most often injected included vaccines and antibiotics [24].

In a study of occupational injuries reported by zoo veterinarians in the United States, needle sticks were the most frequent injury reported, with 86.7% of respondents reporting  $\geq 1$  stick and 50% of these sticks involving vaccines. Eighteen zoo veterinarians (6.5%) reported adverse reactions, including infections, that required medical treatment, although the type of infection or vaccine was not reported [25].

In addition to veterinarians, individuals engaged in animal farming and aquaculture have an occupational risk of exposure to vaccines and vaccine strains. The use of vaccines is increasing because all intensive methods of animal and fish farming magnify the problems associated with infections or endemic diseases in animals because the animals and fish are kept in close proximity to each other. New vaccines are being developed to prevent infection, and some of these try to eliminate the need to administer medications via feedstuff.

The CDC has investigated a report of an illness that followed the unintentional inoculation of a live anthrax vaccine (Sterne) in a 17-year-old woman while she was vaccinating her horse (Michael Bruce, CDC, unpublished data). She sought medical attention both for local symptoms that occurred immediately and for systemic symptoms that occurred during the onset of infection within 24 h after the injection. Neither of 2 blood cultures yielded *B. anthracis*. There have also been reports of infection after unintentional exposure to vaccines, including *Brucella* and Newcastle virus vaccines, and warning labels have been developed for those vaccines [26]. The USDA is currently evaluating requirements for warning labels for veterinary vaccines (Louise Henderson, USDA, personal communication).

Autoinoculation may result in allergic reactions or toxic inflammatory reactions at the site of injection. These adverse side effects are frequently due to the adjuvant, which is utilized to enhance the immune response to vaccine antigens; adjuvants are composed of chemicals, microbial components, or mammalian proteins [27]. Adjuvants may cause adverse side effects by increasing the systemic adverse effects of the vaccine, such as fever; more often, adjuvants may cause local reactions. Some adjuvants allowed in animal vaccines are not allowed in human vaccines, because the tolerance for local inflammatory reactions and the toxicity to tissues is higher in animals than in humans.

Reports of toxic inflammatory reactions in veterinarians and

others who administer vaccines and sustain unintentional injections include reports of reactions to *Mycobacterium paratuberculosis* bacterin, which is used to prevent Johne disease in cattle [28]. Also, if injections occur in a joint, sterile joint abscesses may occur; in 2001, cases occurred following self-injection with a vaccine intended for swine (Steven Mostow, Infectious Disease Society of America [IDSA], unpublished data; John Black, IDSA, unpublished data). Necrosis has been reported in the fingers of 4 veterinary technicians in Turkey who accidentally stabbed their fingers during vaccination of poultry for *Salmonella enterica* serotype Enteritidis. All 4 developed severe inflammation, which led to local tissue necrosis of the finger. In the United States, devices may be used to protect the hands of workers during injection [29].

Individuals involved in aquaculture may also be at risk of self-injection. In a survey of professional teams that routinely inject fish, professional vaccinators reported from 1 to  $\geq 50$  self-injections during a single season [30]. Two cases of hospitalization were reported as having been due to anaphylactic reactions. There was no evidence that any injectors were infected, but there was evidence that the majority of the reactions were inflammatory or allergic in nature. Oil-based vaccines used in the salmon industry have been reported to cause serious tissue necrosis and vascular spasms when self-injected.

## **UNINTENTIONAL, NONOCCUPATIONAL EXPOSURE OF HUMANS TO ANIMAL VACCINE**

Unintentional exposure to vaccine has occurred in children. In addition to the reports describing exposure of children to *Brucella* and *Bordetella* vaccines noted above, there is a published report of a 14-year-old child who drank milk from a gallon inoculated with 21 vials of live virus vaccine intended to immunize 1000 baby chicks against Newcastle disease. The patient was managed with catharsis and remained asymptomatic after a 28-day observation period [31].

## **INTENTIONAL ADMINISTRATION OF ANIMAL VACCINES TO HUMANS**

There is potential concern that vaccines licensed only for animal use are being or may be used intentionally by humans, especially for prophylaxis against diseases for which humans consider themselves at risk but for which no human vaccine has been available (e.g., West Nile encephalitis, Lyme disease, and anthrax). Some vaccines (e.g., rabies vaccine) are distributed only to individuals with a license; other products are readily available to individuals without a veterinary license (e.g., anthrax vaccine). It would be of interest to know whether any individuals self-administered an anthrax vaccine licensed for animal use during the recent anthrax incidents in the fall of 2001 on the

East Coast. Publicity associated with West Nile encephalitis has led to anecdotal reports of individuals who have considered self-administration of West Nile vaccine intended for horses. Would recombinant vaccinia-rabies recombinant vaccine be sought and used intentionally by individuals in an attempt to protect them from smallpox?

There is limited knowledge about intentional administration of veterinary biologic products to humans. A survey of veterinarians registered with the Idaho Board of Veterinary Medicine was conducted in 1999 to assess their knowledge and perception of the intentional administration of veterinary medications to humans; 392 (36.4%) responded [32]. In that survey, systemic antibiotics were among the most frequently reported veterinary medications misused in humans. Of the responding veterinarians, 282 (72%) reported that they had been asked questions by caregivers of animals about the use of veterinary medications in humans, and 274 (70%) reported human misuse of systemic antibiotics and provided specific information on the classes of antibiotics that had been misused. On average, veterinarians suspected that 2.3% of their clients who received prescription medications for their animals administered veterinary medication to themselves, their children, or their friends. Those who were rural residents, those who worked in health care (particularly veterinary health care), and those who had no or inadequate health insurance coverage were among the individuals noted to be most likely to use veterinary medications. The veterinarians speculated that the reasons for use included independent and self-sufficient attitudes, the convenience and availability of the medication, the lower cost of the medication, or the perception that the medication was stronger than the medication administered to humans. The authors suggested that human misuse of veterinary drugs may be more common than many health practitioners realize.

## DISCUSSION

Is human exposure to veterinary vaccines a potential public health concern? There is currently limited understanding of the incidence of exposure of individuals to veterinary vaccines or of the consequences of such exposure. In addition, the potential for exposure and for adverse consequences secondary to exposure to veterinary vaccines may be increasing. The increased development and use of veterinary vaccines (including live vaccines), the increased aerosol administration of vaccines, and the increased proportion of individuals in the United States who are immunosuppressed and who may be exposed to these vaccines or to animals shedding the vaccine strains suggest that increased vigilance may be warranted.

The process for licensure of animal vaccines differs from that for human vaccines, and it is less rigorous. The USDA regulates veterinary vaccines, and the regulations are found in the Virus

Serum Toxin Act in Title 9 of the Code of Federal Regulations [33]. For the purpose of safety, the regulations state that a vaccine should not cause “undue local or systemic reactions”; for efficacy, the regulations state that a biological product “shall with reasonable certainty yield the results intended when used as recommended” [33, section 113.6]. In addition to requirements for safety, efficacy, and purity, the USDA performs a risk analysis before licensure to assess the risk posed by the vaccine to animals, human health, and the environment; the extent of this analysis varies according to vaccine (Louise Henderson, USDA, personal communication). The FDA regulates currently administered human vaccines and vaccines under investigation; there is a lengthy prelicensure process that may involve thousands of individuals in clinical trials.

Surveillance is conducted to monitor adverse effects of vaccines in animals, and problems have been documented [33]. Safety concerns have included instances of failure to inactivate the virus sufficiently, resulting in disease in the vaccinated animals. This has been documented for the foot-and-mouth vaccine, as well as for the Venezuelan equine encephalitis vaccine. In addition, there have been adverse reactions to vaccine that were associated with the residual virulence of the vaccine organisms. The attenuated vaccine strains may be capable of producing disease in immunosuppressed and/or pregnant animals and have occasionally caused disease in healthy animals [33]. There have also been examples of vaccines that induced lethal disease when administered to a species other than the target species [33].

In addition to problems associated with the vaccine virus strain itself, there are numerous examples of vaccines that have been contaminated with extraneous microorganisms, including live *Mycoplasma* organisms and bluetongue virus [33]. In the early 1990s, a modified live virus vaccine containing canine distemper virus, canine parainfluenza virus, canine adenovirus-2, and canine parvovirus was reported to have caused abortion and death when administered to pregnant dogs; the vaccine was found to be contaminated with bluetongue virus [34, 35]. Bluetongue virus causes disease in wild and domestic ruminants, and it was not known to cause natural infection and disease in dogs.

Avirulent live vaccines are considered more efficient for preventing the spread of some diseases, such as those due to *Salmonella* infection in poultry raised for human consumption. A French study of several isolates of 3 live vaccine strains of *S. enterica* serotype Typhimurium demonstrated that the vaccine strains in the environment of the inoculated animals persisted for at least 1 month after vaccination [36]. Some vaccine strains persisted in the liver and gut of poultry for at least 10 days. Two of the 3 strains, including 1 commercially available in the United States, showed evidence of genetic instability, but the investigators were unable to link the genetic changes to an

impact on safety [37]. A number of issues are raised by such studies, including the public health impact, if any, of animals raised for human consumption that are infected with a vaccine strain at the time of slaughter, the potential impact of the persistence of the virus in the environment, and the uncertainty posed by the genetic instability of some veterinary vaccines.

When physicians see patients with a zoonosis and query about exposure to sick animals, they may also want to query about exposure to live vaccines, to the environment in which live vaccines are administered, or to animals to which live vaccine has recently been administered. Occupational studies of exposure and outcome may be useful. More information is needed regarding the potential misuse of veterinary vaccines. Human misuse may be more common than many health practitioners realize. In 1998, the National Poison Control Center (Washington, DC) registered >3700 adverse events associated with human use of medications intended only for animal use.

Veterinarians should be instructed to take precautions to avoid exposing themselves or others who are in proximity to the animals to the vaccine (e.g., inadvertent administration of aerosol vaccine to an unsuspecting pet owner). Should immunosuppressed patients be warned to decrease the risk of exposure to aerosol and non-aerosol formulations of live vaccines? Should warning labels be placed on veterinary vaccines to avoid human exposure, and should individuals be aware that human safety studies have not been conducted? To what agency or organization should illness suspected to have resulted from human exposure to veterinary vaccines be reported? Should there be more safety testing, including increased testing of the genetic stability of the vaccine strain? Those who use veterinary vaccines should understand potential human health hazards and should know to whom to report suspected adverse consequences of exposure.

Veterinary vaccines have provided enormous economic and health benefits to the animal industry, and they have dramatically reduced the incidence of many zoonotic infections in humans. At the same time, as the frequency and administration of animal vaccines increase, we must be vigilant regarding human exposure and safety. Health consequences of human exposure to animal vaccines or vaccine strains cannot be quantified if they are not recognized and reported. For some diseases, such as brucellosis and vaccinia, a link has been clearly documented. For others, such as disease due to *B. bronchiseptica* infection, additional study to establish whether a link exists is needed. Some form of postmarketing surveillance for human adverse events should be considered when new vaccines are introduced, especially live vaccines for zoonotic diseases. Awareness of the potential for adverse events after exposure to animal vaccines or to animals vaccinated with a live vaccine should increase among physicians, and robust mechanisms of

reporting, in addition to follow-up investigation, should be developed and implemented for suspected adverse events.

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