Recommendations of a national working group on prevention and control of rabies in the United States

Article I: Prevention and education regarding rabies in human beings

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Summary: Substantial changes in the epizootic characteristics of rabies have transpired in the United States during the past 50 years. Traditional veterinary practices and public health recommendations have effectively controlled rabies in dogs and prevented associated human fatalities; however, they have been unable to adequately address the problem of rabies in wildlife. Attributable in part to a renewed focus on emerging infectious diseases, a conference was held at the Centers for Disease Control and Prevention in 1993 to begin discussion focused on the reemergence of rabies and to formulate new suggestions for prevention and control of rabies in the United States. Three major working groups were formed from a national committee of professionals representing a broad array of biomedical disciplines. These groups concentrated on prevention of rabies in human beings, education, laboratory diagnosis of rabies, and rabies control in animals. The groups described the perceived minimum requirements to promote prevention and control of rabies in the United States into the next century. The following article describes the needs and recommendations identified by the prevention and education working group. Two other articles, scheduled for the Nov 15 and Dec 1, 1999 issues of *JAVMA,* will relay the needs and recommendations of the working groups on laboratory diagnosis of rabies and rabies in wildlife.

Rabies remains one of the most important zoonoses in the United States. Despite its historic incidence, public health importance, and epidemiologic extent, a unified national plan does not exist for prevention and control of rabies. The reemergence of a well recognized infectious disease such as rabies may be partially attributable to changes in use of land, demography and behavior of human beings, increased travel of human beings, microbial adaptation, and reduced support for appropriate prevention measures.[1,2] In the past decade, rabies in animals—now principally among wildlife rather than domestic dogs—has reached historically high percentages,[3-8] particularly among raccoons[4] and coyotes.[9,10]

An increase in rabies in animals presents an increased risk of human exposure. Consequently, there has been an increase in the necessity for **postexposure prophylaxis (PEP)**,[11-15] although precise quantification of such an increase is poor. Moreover, current cases of rabies in human beings have developed, not because of vaccination failures, but because of apparently unrecognized exposures from bats[16-20] or the risks that such exposures may pose. This observation has led to a controversial recommendation concerning the consideration of PEP in human beings after possible exposure to bats,[21] which tries to balance the effectiveness of prophylaxis against the low risk of disease acquisition associated with many of these events. Although the primary objective of this recommendation is to prevent human mortality, recognizably it may also lead to an additional increase in PEP and may not be cost-effective.[22,23]

Clearly, the apparent health threat from rabies has changed substantially during the past several decades in that the current leading reservoir, the raccoon, is an adaptable wild animal that interfaces closely with human beings in suburban and urban settings. As land development increases throughout the country, particularly in the eastern United States, human beings are more likely to interact with animals and engender a predisposition toward conservation of certain wildlife rather than replacement or displacement. In addition, the translocation of wild animals, such as raccoons and coyotes, by human beings for recreational and consumptive use has contributed to epizootics. Moreover, recent evidence suggestive of viral adaptation[17] may be associated with an increase in rabies in human beings because of a particular rabies virus variant in bats.

An increase in rabies in animals demands the capacity for efficient diagnosis. Diagnostic training, ensuring availability of reliable commercial reagents, and continuing medical, veterinary, and other professional education, are fundamental components of prevention and control of

rabies in the United States. Historically, diagnostic material, training courses, and reference reagents were routinely provided by the **Centers for Disease Control and Prevention (CDC)**. At present, participation in diagnostic proficiency testing for rabies is voluntary, and slides are supplied for a fee by the Rabies Proficiency Testing Program of the Wisconsin State Laboratory of Hygiene. Reference reagents are no longer regularly provided by the CDC to state public health or agricultural laboratories. Commercial diagnostic reagents are periodically in short supply for several months. Furthermore, rigorous formal laboratory training in diagnosis of rabies is neither frequent nor widely available, which is in contrast to the 1970s, when diagnostic training courses were offered annually by the CDC. Every several years, attempts are made to offer training courses at various state rabies laboratories with the CDC, the National Laboratory Training Network, and associated additional professional participation. The inevitable effect of decentralization has been the limitation of communication among rabies diagnostic laboratories and the divergence of laboratory methods from a standard diagnostic protocol. In addition, awareness of the incidence of rabies in human beings and appropriate clinical application of diagnostic tests has declined in the biomedical community. Many recent cases of rabies in human beings have been diagnosed late in the clinical course or during postmortem examination,[16] leading to delayed case investigation and administration of PEP to people whose exposure may have been prevented through earlier clinical suspicion, diagnosis, and appropriate precautions. Enhanced support for continuing medical education, diagnostic training, and activities to ensure reliable commercial reagents is a fundamental need for prevention and control of rabies in the United States.

Despite substantial changes in the epizootic characteristics of rabies after the successful control of development of the disease in dogs, regulations responsible for this historic accomplishment have not always been adequately updated to reflect the wildlife component of the current rabies problem or future expectations. Part of the complexity of prevention and control methods lies with the inherent variability in authority by the agencies responsible for public health, agriculture, and wildlife.

At one time, all cases of rabies were compiled and reported by the USDA Bureau of Animal Industry (dissolved in 1955, now the Animal and Plant Health Inspection Service, USDA). In the 1950s, the USDA Agriculture Research Service, Animal Disease Eradication Division, Special Diseases Eradication Section, was responsible for collection and compilation of data regarding rabies cases and numerous control activities pertaining to rabies in domestic animals, then principally among dogs. In 1960, the establishment of the National Rabies Laboratory at the Communicable Disease Center (now known as CDC), United States Public Health Service, resulted in a transfer of responsibility for data collection and analysis, as well as diagnosis and prevention activities. In addition to conducting surveillance and epidemiologic investigations during the past 40 years, the CDC has an expanded role in laboratory and field research, with an emphasis on molecular methods and control techniques, including research on rabies vaccination in wildlife beginning in the 1960s.[24,25] These continued activities are in keeping with the mission of the CDC within the National Centers for Infectious Diseases in promoting health and quality of life by preventing and controlling infectious diseases. With the starkly contrasting epidemiologic shift in rabies from domestic animals to wildlife, there is a need for greater involvement of federal and state health, agriculture, wildlife, and conservation agencies in the design and application of potential control strategies. Additionally, the historic role of the USDA, in predator control to limit damage to livestock by wildlife and in control of rabies among domestic dogs, provides support for renewed involvement in future control activities. Close coordination between multiple local, state, and federal entities will be necessary for updating current regulations and formulating novel control strategies. These problems will require diligent attention and dedicated effort to maintain and advance the concept and application of prevention and control of rabies in the United States.

Trends in Postexposure Prophylaxis

One of the objectives of the national "Healthy People 2000" [26] plan was to decrease the need for PEP in the United States by 50%. Although instances of PEP are not generally reportable, substantial increases have been documented in areas newly affected by rabies in terrestrial animals, such as raccoons. For example, in New York, reports of PEP increased from an average of < 100/y prior to 1990, which was before the arrival of the rabies epizootic in raccoons, to > 3,000 in 1993.[7,15] A similar increase in PEP has been reported in Connecticut.[12] Nationwide, it is estimated that PEP is administered annually to between 20,000 and 40,000 people.[3,6,27] A better understanding of the circumstances precipitating PEP, and the incidence by region and season, would facilitate planning to ensure that adequate biologics are available. In addition, these data would help officials focus educational efforts to specific at-risk audiences, thereby reducing exposures and the resulting need for the consideration of PEP.

A national mechanism for tracking or analyzing the incidence of PEP is not currently in place. Previously, rabies biologics were usually obtainable only through state health departments, which

facilitated the compilation of epidemiologic information. A few states still try to control the disbursement of rabies biologics; thus, they retain a stringent oversight of PEP, partially in an effort to decrease unnecessary use.

Educational efforts to reduce PEP, assurance that it is administered properly, and monitoring and assessment of the adequacy of current **human rabies immune globulin (HRIG)** supplies are inherently weak. A national or regional PEP surveillance and reporting program is necessary to monitor these trends.

Recommendations—Surveillance of PEP could considerably improve current methods of rabies prevention in the United States. Tracking PEP as reportable events or conditions, such as for rabies cases, could be conducted by the CDC on a national or regional basis. Passive surveillance should be initiated through recommended reporting of related animal bites and PEP, so the latter's administration could be tracked and analyzed on a state-by-state basis. Selected active surveillance or special studies should be initiated in limited areas or regions for extrapolation to larger human populations at risk. These efforts may consist of prospective studies at urgent care or emergency rooms or retrospective analysis of preexisting databases, such as those of health care organizations and states that maintained records of PEP.

Status of Rabies Biologics

Recent developments in rabies biologics include the licensing of a purified chick embryo culture vaccine,[28,a] the addition of a prolonged heat-treatment step during processing of 1 of the HRIG products, and a name change from Imogam Rabies to Imogam Rabies-HT.[b] Because most of the worldwide HRIG market is dominated by a single manufacturer (although there is a second manufacturer in the United States[21]), there may be severe constraints on the manufacture of products of human origin. Examples of such problems include the restricted availability of HRIG because of the institution of new screening techniques for recognized adventitious agents (eg, hepatitis C virus), emergence of novel adventitious agents, or catastrophic emergencies affecting product supply or production. In the event of an HRIG shortage, present options are extremely limited and inferior. The formulation of a contingency plan in the event of an HRIG shortage is critical. Without HRIG, PEP would be limited to vaccine-only treatment that, although recommended by the World Health Organization for certain limited exposures,[29] is not included in the current recommendations of the United States **Advisory Committee on Immunization Practices (ACIP)**. This vaccine-only regimen may be effective in some cases, but it is not as efficacious as when HRIG is combined with vaccine, particularly following severe bite exposures. A second option could be to substitute heterologous immune globulin for HRIG. In the United States, antirabies serum from horses was used in this manner until gradually replaced by HRIG in the mid-1970s. The emergency substitution of a new-generation purified **equine rabies immune globulin (ERIG)** product, considered for use in other countries, may be an alternative option for the United States; advances in commercial manufacturing have resulted in much lower extraneous protein concentrations and considerably fewer adverse reactions.[30-33] Moreover, the efficacy of combined vaccine and purified ERIG treatment is superior to vaccine-only treatment in preventing rabies in human beings.[29]

Recommendations—Plans for a compassionate Investigational New Drug proposal for alternative use of purified ERIG, commonly used in developing countries, should be prepared by the CDC, filed with the FDA, and be initiated in the event of an acute HRIG shortage. Research to develop alternatives to HRIG, such as monoclonal antibodies, should be encouraged and financially supported for eventual licensure.

Update of Recommendations of the Advisory Committee on Immunization Practices

The ACIP periodically updates a reference document that provides guidance for preventing rabies in human beings.[21] In the ACIP recommendations, an exposure is clearly and succinctly defined. However, common practice in exposure assessment has evolved to favor treatment in highly theoretical potential exposure scenarios.[12,15,34] These situations typically involve indirect nonbite exposure through hypothetical contact-transfer of rabies virus via a pet or inanimate object, conditions under which natural infection in human beings has not been described. Management of previously vaccinated persons often involves routine booster inoculations, sometimes more frequently than recommended, rather than serologic monitoring and boosting as necessary when a decline in titer is detected.[21] Previously vaccinated persons are, in some cases, assessed as being repeatedly exposed through nonbite routes. Management of these individuals can often vary. Furthermore, guidelines for the confinement and observation of biting animals have only recently been extended from cats and dogs to ferrets, based on relevant scientific research detailing viral shedding.[35,36] Support for relevant research and risk assessment

would facilitate better management of situations, such as exposure to bats, in which rabies may be a factor.[21]

More definitive guidance for determining the need for PEP in nonbite exposure situations is critically needed. More information regarding the interpretation of serologic results and the recommended frequency of booster doses and PEP for repeatedly exposed vaccinated persons is desirable.

Recommendations—A comprehensive, user-friendly algorithm for suspected nonbite rabies exposures should be developed. Research to determine appropriate rabies vaccination standards, such as the need for serologic testing or booster doses of rabies vaccine, should be promoted. More detailed information related to repeated exposures of previously vaccinated persons (eg, wildlife rehabilitators) and the frequency of appropriate PEP, especially in nonbite settings, would be desirable.

Compliance with Current Postexposure Prophylaxis Regimens

The current PEP regimen for a person who has never received rabies vaccine consists of administration of HRIG on day 0 and vaccine on days 0, 3, 7, 14, and 28.[21] Deviations from recommended schedules and cessation of PEP are reported, but the extent and frequency of noncompliance are not well described. A simplified regimen would be expected to increase compliance and reduce cost and adverse events. Novel, future vaccines (eg, DNA vaccines[37]) and the ease of their delivery would facilitate simpler PEP schedules and possibly the reconsideration for the necessity or elimination of HRIG.

Recommendations—The source and extent of noncompliance with PEP schedules should be investigated. General procedural recommendations for managing interruptions and alterations of PEP schedules should be outlined. Alternative PEP schedules should be investigated in relevant animal models and in mock clinical trials in humans with nonexposed volunteers for serologic and safety evaluation. Novel biologics should be developed to facilitate abbreviation of the PEP schedule and decrease the necessity of HRIG.

Educational Issues

Rabies in human beings in the United States is rare, but daily consideration of its prevention is not. The public health impact of rabies in wildlife could be reduced through educational efforts that describe, in practical terms, how to recognize and avoid exposure to rabies.[21] Determining potential exposure to rabies, and thus the need for PEP, accounts for a substantial portion of the rabies-related consultations by public health and medical professionals, especially in presumed human-bat interactions. Better communication is also needed to educate the public about traditional control measures for rabies (eg, primary vaccination) in domestic animals; this is particularly true in cats, which are the most commonly reported rabid domestic animal in the United States.

Better tools for more consistently assessing exposure to rabies are essential. The development of general and specific educational material for a number of target audiences is critically needed. A resource manual for determining exposure to rabies is desired for use in state and local agencies.

Recommendations—A PEP decision tree wall poster could be developed for use in emergency and urgent care facilities. Videotapes, brochures, and interactive computer software addressing the complex problem of rabies should be developed. A technical manual (notebook) describing human exposures to rabies should be compiled and routinely updated. Educational campaigns should be developed for persons who are at an increased risk for exposure to rabies (eg, veterinarians, animal control workers, primary care physicians) and for facilities and events that may bring members of the public to increased risk of contact with animals (eg, summer camps, fairs, animal exhibits), particularly wildlife. The CDC should act as a “clearinghouse” to facilitate solicitation and redistribution of existing educational materials from states; furthermore, the CDC should assume responsibility for the development of brochures, videotapes, manuals, and an Internet Web site. Routine vaccination of companion animals needs continual emphasis, particularly in cats. Mechanisms to evaluate the effectiveness of educational efforts should be sought. Mass media resources, such as television and radio, should be used more often to disseminate proper rabies education messages.

Since the meeting of the working group in 1995, initiatives proposing the tracking of PEP have been formulated but have been unsuccessful in achieving this goal. On a positive note, the ACIP recommendations were updated and published in January 1999.[21] Alternatively, investigation of incidence and severity of deviation from the recommended PEP schedule, as well as alternative schedules, has not progressed. One of the greatest advances has been the compilation and publication of a well received “Bats and Rabies” brochure, which was a

collaborative effort between the CDC, the US Fish and Wildlife Service, and Bat Conservation International. Also, the CDC now has a comprehensive Web site that includes a related site just for children (www.cdc.gov/ncidod/dvrd/rabies).

Preview of Article II

Article II, which will be published in the Nov 15, 1999 issue of *JAVMA*, discusses laboratory practices currently in use to test potentially rabid animals, direct fluorescent antibody testing, diagnostic reagents, and capabilities for typing rabies strains.

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[a]RabAvert, Chiron Behring GmbH & Co, Emeryville, Calif.
[b]Imogam Rabies-HT, Pasteur-Merieux Serum et Vaccins, Connaught Laboratories Inc, Swiftwater, Pa.

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