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Safety of Lyophilized SAG2 Oral Rabies Vaccine in Collared Lemmings

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ABSTRACT: Fifteen collared lemmings (*Dicrostonyx groenlandicus*) were exposed to a lyophilized oral rabies vaccine designed to immunize wild carnivore populations. No animals contracted rabies from the vaccine as determined by the absence of clinical signs after 37 days and lack of rabies virus in brain tissue determined by the fluorescent antibody (FA) test. These results suggest that collared lemmings would not contract rabies if they ingested this lyophilized vaccine in the wild during bait vaccination programs for arctic foxes (*Alopex lagopus*).

Key words: collared lemming, *Dicrostonyx groenlandicus*, SAG2, rabies, oral vaccination, pathogenicity.

The use of bait vaccination programs has become a widespread and effective means to control rabies in several wild carnivore populations (Wandeler, 1988, 1991; MacInnes, 1988; Bogel et al., 1992). Thus far, all oral vaccination trials and programs in the field have used liquid vaccines that are susceptible to freezing if distributed during cold weather. This would occur in northern circumpolar regions where freezing air and ground temperatures can be encountered throughout the year but especially from September through May. Should the vaccine bypass the buccal and pharyngeal mucosa in a frozen state, the vaccine may be inactivated by the acidity and presence of proteolytic enzyme in the stomach (Wandeler, 1991). With currently recommended bait-vaccine applications twice per year (World Health Organization, 1992), in spring and fall, there is obvious potential for the vaccine freezing prior to ingestion, thereby frustrating expensive and time consuming programs. It was for this reason that a lyophilized vaccine that would not be deleteriously affected by freezing ambient conditions was made

available to evaluate in the principle vector of rabies in the arctic, the arctic fox (*Alopex lagopus*) (Rausch, 1958; Ritter, 1981; Cherkasskiy, 1990; Crandall, 1991). The potential for controlling rabies in the arctic fox has been considered over the past 20 yr (Follmann et al., 1987, 1988, 1992; World Health Organization, 1990). Two liquid oral vaccines, SAD-BHK₂₁ and SAG1, were found to be effective in immunizing captive foxes (Follmann et al., 1988, 1992). Recently, a lyophilized version of the SAG2 vaccine, a double deletion mutant (Lafay et al., 1994), was found to protect captive arctic foxes as determined by production of rabies-specific antibody and survival following challenge with the arctic variant of rabies virus (E. H. Follmann, unpubl. data).

It is essential that oral vaccines do not induce rabies in non-target vertebrate populations who become exposed to the modified live virus vaccines used in field applications. Initiating a rabies epizootic in a non-target population would not be acceptable and could have serious public health concerns. SAG1 and SAG2 liquid vaccines were found to be safe in six species sympatrically distributed with the arctic fox including mink (*Mustela vison*) and five species of rodents (Follmann et al., 1996). Despite the collared lemming (*Dicrostonyx groenlandicus*) having been shown to safely ingest liquid SAG1 vaccine, it was felt important to evaluate the solid lyophilized form of SAG2 vaccine also. This because of the high probability of total ingestion of the vaccine compared with the liquid vaccine, some of which would leak onto the ground once the capsule containing the vaccine was opened.

Representatives of the other five species were not available for lyophilized vaccine trials. However, to ensure the safety of a program to immunize arctic foxes, it would be appropriate to evaluate the lyophilized vaccine in other nontarget species.

Fifteen collared lemmings from a captive population at the UAF were caged individually in a Biosafety Level 3 Facility of the UAF Experimental Animal Facility. Lemmings were fed Rabbit and Lab Chows (Ralston Purina Co., Checkerboard Square, St. Louis, Missouri, USA), lettuce, carrots, and sunflower seeds. The lyophilized vaccine was provided by Virbac Laboratories (13-eme Rue-L.I.D., 06516 Carros-Cedex, France). The titer of the vaccine was $\text{MLD}_{50}:10^{-5.5}/0.01$ ml determined in suckling CD-Ha/ICR mice at the Alaska State Virology Laboratory (ASVL; Fairbanks, Alaska, USA). A vaccine wafer (about $2.5 \times 2.5 \times 1$ cm) without any coating was placed in each cage. Any remaining at 4 days was removed from the cages and lemmings continued on standard rations. The titer of vaccine removed from cages was not determined because in some cases it was in poor condition having absorbed moisture from food and bedding. Lemmings were maintained for 37 days at which time they were deeply anesthetized with Metofane (Pitman-Moore, Inc., Mundelein, Illinois, USA) and blood collected via cardiac puncture, which also served to euthanize the animals.

Following euthanasia touch impressions of brain were analyzed for rabies virus antigens using direct FA (Goldwasser and Kissling, 1958) at the ASVL. Sera were analyzed for rabies antibody using the RFFIT (Smith et al., 1973) at the Kansas State University Department of Veterinary Diagnosis (Manhattan, Kansas, USA). Animal care and the experiment were approved by the University of Alaska, Fairbanks Institutional Animal Care and Use Committee.

Seven lemmings ate the entire wafer (3 within 24 hr, 1 within 48 hr, 1 within 72 hr, and 2 within 96 hr); five some of it and

three none of it. One lemming died 22 days after eating (within 24 hr of exposure) the entire wafer. Brain tissue was negative for rabies virus; serum was not available for analysis and a necropsy was not performed. The remaining 14 lemmings survived until day 37. All were negative for rabies virus in brain tissue, and 12 were negative for rabies antibody. Two lemmings had seroconverted with values of 0.3 and 0.4 IU ml^{-1} , the former having eaten about one-half and the latter the entire wafer. However, these low titers could have resulted from cross-reactions rather than from the presence of rabies antibody.

These results provide additional support for using the lyophilized SAG2 oral rabies vaccine in arctic and subarctic regions. None of the lemmings showed clinical signs of rabies during a 37-day period and none had rabies virus in brain tissue. The presence of antibody in the blood of two lemmings, although of low titer and perhaps a result of a cross reaction with other antigens, may provide additional evidence of the safety of this highly attenuated vaccine. Collared lemmings exposed to liquid SAG1 vaccine in an earlier trial did not develop antibodies (Follmann et al., 1996). Since rabies has not been recorded in collared lemmings such protection would not appear to provide any advantage to these animals.

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