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Short communication

# Cattle rabies vaccination—A longitudinal study of rabies antibody titres in an Israeli dairy herd

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ABSTRACT

In contrast to many regions of the world where rabies is endemic in terrestrial wildlife species, wildlife rabies has been controlled in Israel by oral rabies vaccination programs, but canine rabies is re-emerging in the northern area of the Golan Heights. From 2009 to 2014 there were 208 animal rabies cases in Israel; 96 (46%) were considered introduced primary cases in dogs, triggering 112 secondary cases. One third (37/112) of the secondary cases were in cattle. Rabies vaccination is voluntary for cattle in Israel, except those on public exhibit. Rabies vaccination schedules for cattle vary based on farm practices and perception of risk. In this study 59 cattle from a dairy farm which routinely vaccinates against rabies were assigned into six groups according to age and vaccination histories. Four groups contained adult cows which had received one previous rabies vaccination, one group of adults had received two previous vaccinations, and one group was unvaccinated calves. Serum samples were collected and the cows were vaccinated with a commercial rabies vaccine. Sera were again collected 39 days later and the calf group re-vaccinated and re-sampled 18 days later. Sera were analyzed for the presence of rabies virus neutralizing antibodies using the rapid immunofluorescent antibody test. Cattle with antibody titres ≥0.5 IU/ml were considered to be protected against rabies. Twenty-six of 27 adult cattle (96%) vaccinated once at less than five months old did not have protective titres. Sixty percent (6/10) cattle vaccinated once at around six months of age did have adequate titres. Cattle previously vaccinated twice ($n = 10$; 100%) with an 18 month interval between inoculations, had protective titres and protective antibody titres following booster vaccination ($n = 51$; 100%). The anamnestic response of cattle to a killed rabies vaccine was not affected by the time interval between vaccinations, which ranged from 12 to 36 months. These results suggest that calves from vaccinated cows should not be vaccinated before six months old to avoid maternal antibody interference. Whilst most cattle older than six months old will be protected after a single inoculation, a second inoculation ensures a higher antibody levels for improved protection. Cattle receiving an effective priming dose responded well to a booster up to 36 months later. Such results demonstrate the effectiveness of rabies vaccination in cattle and the added value of a second dose to ensure a prolonged immune response against rabies.



## 1. Introduction

Rabies is a fatal viral disease which causes human deaths and affects livestock production in endemic countries. Although safe and effective rabies vaccines exist for humans and animals, rabies results in approximately 61,000 human deaths each year worldwide (WHO, 2013; Taylor, 2013). Rabies is caused by a virus of the family Rhabdoviridae that infects mammals (including bats). It is an acute viral infection that is almost invariably fatal once symptoms develop. The virus is found in saliva of infected animals and is most often transmitted through a bite wound (Kahn et al., 2010).

Rabies remains a disease of significant public health importance as humans exposed to the virus must receive post-exposure prophylaxis which is a costly medical expenditure. Human exposure to the rabies virus is often due to direct contact with an

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infected bat, cat or dog. Globally, unvaccinated dogs are the primary source of infection leading to the majority of humans deaths due to rabies (Taylor, 2013). However, infected livestock, particularly cattle, provide a considerable risk to veterinarians and handlers, especially when neurological signs of rabies in cattle are confused with signs of choking (Hanlon, 2013).

Cattle grazing on pasture as well as those housed in confinement are at risk of rabies exposure. Depending on their location unvaccinated cattle can be infected with the virus through the bite of a rabid raccoon, fox, or skunk in North America; a vampire bat feeding in Latin America; or following an attack by a roaming dog in many other regions of the world (particularly the Middle East, Africa and Asia). In the Middle East, unvaccinated dogs and wildlife reservoir species (i.e., red fox and golden jackal) can transmit the virus to cattle. A recent recalculation of the global rabies burden estimates 32,000 cattle are lost annually to this disease (Shwiff et al., 2013).

In Israel, wildlife rabies has been under control at a national level through the use of oral rabies vaccines distributed into the environment since 1998 (Yakobson et al., 2006). Thus, infrequent cases in foxes and golden jackals occur as spillover from infected dogs or at the borders with rabies endemic countries. In Israel, dog vaccination, microchip identification and registration are mandatory with records kept in an electronic database. However, since 2004, an incursion of canine rabies has occurred in northern Israel resulting in rabies cases reported in unvaccinated dogs and other species (David et al., 2009; David and Yakobson, 2011). This event has led to spillover cases in cattle, particularly in farms located in the Golan Heights area (see Fig. 1). In this region of Northern Israel there are approximately 25,000 beef cattle and 25,000 dairy cattle. From 2009 to 2014 there were 208 animal rabies cases in Israel; 96 (46%) were considered introduced primary cases in dogs, triggering 112 secondary cases. One third (37/112) of the secondary cases were in cattle.

Prophylactic vaccination against rabies is recommended for cattle in rabies endemic areas (OIE, 2014). Licensed rabies vaccines exist for cattle but recommendations vary by manufacturer as to minimum age of vaccination and number of doses required. Actual application of commercial vaccine may vary farm to farm based on experience and herd health practices. In Israel, voluntary cattle vaccination rates are low due to an often incorrect perception of low exposure risk. Vaccination of cattle against rabies is required by law under specific situations, such as cattle that will be in close contact with humans (i.e., on display, or attending fairs and exhibitions; Israel Ministry of Agriculture and Rural Development, 1934). In many countries, including Israel, cows producing milk for human consumption are routinely voluntarily vaccinated against rabies for public health reasons. In Israel, detection of rabies in a cattle herd activates quarantine measures for the herd based on vaccination status. Herds with current vaccination status are quarantined for 45 days and unvaccinated herds quarantined for 90 days (Ezra, 2007).

Successful pre-exposure vaccination of cattle against rabies using inactivated commercial rabies vaccines is well documented (Carneiro et al., 1955; Blancou et al., 1984; Silvonen et al., 1994; Benisek et al., 2000; Anderson et al., 2014; Gilbert et al., 2015). Rabies cases reported in vaccinated cattle are most often related to product use variables including wide-ranging immunization protocols and booster recommendations (Rodrigues da Silva et al., 2000; Albas et al., 1998; Filho et al., 2012). A strong correlation between circulating rabies antibody titres in cattle and protection against rabies has been previously documented (Blancou et al., 1984). The presence of virus neutralizing antibodies in cattle post-vaccination is indicative of a vaccine's effectiveness (Atanasiu, 1973) and levels of at least 0.5 IU/ml are considered to be protective based on European standards (European Directorate for the Quality of Medicines and Healthcare, 2015). In herbivores, as a minimum requirement, rabies vaccine efficacy can be demonstrated by serology (European Directorate for the Quality of Medicines and Healthcare, 2015).

This study compared rabies virus neutralizing antibody titres between groups of dairy cattle receiving single or multiple doses of a commercial killed virus and adjuvanted rabies vaccine, Rabisin™ (Merial SAS, Lyon, France). The objective was to determine: whether calves fed blended colostrum from vaccinated dams and vaccinated at 4–6 months of age against rabies can mount a strong serological immune response; whether a single dose of vaccine provides at least 12 months of protection as measured by serology; and whether subsequent vaccination (booster) can attain protective rabies titres in young and adult cattle with variable time points between doses.

## 2. Materials and methods

This study occurred during May–July 2013 and in a privately-owned dairy herd of around 600 Friesian cattle (350 milking cows plus 250 followers) located at Moshav Ramat Magshimim, an Israeli settlement in the southern Golan Heights. It was performed under veterinary supervision with animal care and use approval from the Animal Welfare Committee (IACUC), Kimron Veterinary Institute. Cattle on this farm are identified at birth with tattoos, microchip, and/or ear tags. Vaccination and production records are kept electronically (Ezra, 2007). Preventative herd health measures include rabies vaccination and vaccination records are maintained for the life of each cow. Calves are removed to individual housing as soon as possible after parturition, and fed pooled colostrum.

The study focused on: (1) the serological responses of cattle after an initial rabies vaccination and various elapsed time intervals; and (2) the serological response of cattle to a subsequent (booster) rabies vaccination given at various time intervals after the primary vaccination; and (3) the serological immune response of calves vaccinated at four months old and (4) the serological responses of cattle which had received two rabies vaccination more than one year previously and their response to a booster rabies vaccination.

Using the farm's animal records (Ezra, 2007), 59 cows of varying ages were selected for the study according to the following procedure. The initial selection criteria were that animals must have been born on the farm and must have complete vaccination histories. Next, animals were identified that had received just one previous vaccination and these were stratified according to the time since that single vaccination. From the resulting strata cows were randomly selected for study groups A–D (Table 1). An additional 10 cows were randomly selected from cows that had received two previous vaccinations (group E) and eight unvaccinated calves were randomly selected to form study group F (Table 1). Thus, four of the study groups (A–D) had received only one previous rabies vaccination at different ages (i.e., 3–4 months/groups A and C; 6 months for groups B and D) before the study, one group (E) had received two previous vaccinations and one group (F) were calves that had not yet received any vaccinations.

On day 0 cattle in all groups except group F (calves) were serologically tested and then all groups were vaccinated. In the case of the calf group (group F), this was their first vaccination. Serum antibodies in all groups were re-tested 39 days later, and the calf group (group F) received a second rabies vaccination. The calves' antibody levels were then re-tested 18 days later. In summary, during the course of the study cattle in all groups received a pre-booster serological test, a booster vaccination and a post-booster serological test (Table 1). Cattle in groups A–D had received one previous rabies vaccination, were bled and revaccinated on day 0 of the study