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Antibody response of cattle to vaccination with commercial modified live rabies vaccines in Guatemala

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ABSTRACT

Vampire bat rabies is a public and animal health concern throughout Latin America. As part of an ecological study of vampire bat depredation on cattle in southern Guatemala, we conducted a vaccine seroconversion study among three dairy farms. The main objectives of this cross sectional and cohort study were to understand factors associated with bat bites among cattle, to determine whether unvaccinated cattle had evidence of rabies virus exposure and evaluate whether exposure was related to bat bite prevalence, and to assess whether cattle demonstrate adequate seroconversion to two commercial vaccines used in Guatemala. In 2012, baseline blood samples were collected immediately prior to intramuscular inoculation of cattle with one of two modified live rabies vaccines. Post vaccination blood samples were collected 13 and 393 days later. Sera were tested for rabies virus neutralizing antibodies (rVNA) by the rapid fluorescent focus inhibition test (RFFIT). Across two years of study, 36% (254/702) of inspected cattle presented gross evidence of vampire bat bites. Individual cattle with a bat bite in 2012 were more likely have a bat bite in 2013. Prior to vaccination, 12% (42/350) of cattle sera demonstrated rVNA, but bite status in 2012 was not associated with presence of rVNA. Vaccine brand was the only factor associated with adequate rVNA response of cattle by day 13. However, vaccine brand and rVNA status at day 13 were associated with an adequate rVNA titer on day 393, with animals demonstrating an adequate titer at day 13 more likely to have an adequate titer at day 393. Our findings support stable levels of vampire bat depredation and evidence of rVNA in unvaccinated cattle. Brand of vaccine may be an important consideration impacting adequate rVNA response and long-term maintenance of rVNA in cattle. Further, the results demonstrate that initial response to vaccination is associated with rVNA status over one year following vaccination.

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1. Introduction

Rabies is caused by infection with negative sense single stranded RNA viruses in the genus *Lyssavirus*. Rabies virus is the most relevant member from an epidemiological perspective, due to an estimated global human burden in excess of 55,000 cases annually (Knobel et al., 2005). While the global human burden is principally associated with transmission cycles involving domestic dogs, bats are an important reservoir and vector of rabies in the Americas. Rabies outbreaks in cattle have been reported since the early 20th century (Carini, 1911; Haupt and Rehaag, 1921). Carini (1911) linked the outbreaks in cattle to wildlife, as cases in dogs were rare at that time and canine population reduction had no effect on the incidence of cases in cattle. Haupt and Rehaag (1921) were able to isolate the virus from a fruit bat (*Artibeus lituratus*), providing the first evidence linking rabies in cattle with bats. However, it was not until an outbreak in Trinidad that rabies virus (RABV) was isolated from several naturally infected common vampire bats (*Desmodus rotundus*) and linked to the disease in cattle and man (Pawan, 1936). Thereafter, cattle rabies was widely recognized in Latin America, with estimated annual mortality of 0.5 million cattle and annual economic losses of $47 million 1967 USD (~$335 million 2014 USD; www.bls.gov) despite estimated annual vaccination of 2.7 million cattle (Acha, 1967). Cattle continue to be the primary sentinel animal associated with RABV circulation in vampire bats and outbreaks throughout Latin America. One study from Mexico demonstrated a mean mortality rate of 10.3% among affected herds with 50 or more animals, with a range of 1.3% to 29% (Prieto and Baer, 1972). As vaccination campaigns have reduced the burden of canine rabies in Latin America, *D. rotundus* has become the primary reservoir and vector of rabies (Schneider et al., 2009). These obligate blood feeders prefer cattle as a prey resource (Greenhall, 1988), though there can be dietary flexibility where cattle are scarce (Delpietro et al., 1992).

Experimental evidence supporting the utility of vaccination to protect cattle against bat rabies appear as early as 1955 (Carneiro et al., 1955), and modified live or nervous tissue vaccines were shown to reduce mortality of cattle on affected farms during outbreaks (Prieto and Baer, 1972). However, vaccination coverage among cattle, as a preventative measure against rabies infection, tends to be low (<5%) throughout most of Latin America (OIE, 2013), likely due to the relatively high cost of vaccinating large numbers of animals, turnover in herd animals across years, and low perceived threat of rabies among farmers. In Guatemala, the cattle population reported to OIE from 2005 to 2012 fluctuated between 2.0 and 4.5 million animals, with highest estimate in 2009 and lowest in 2012 (OIE, 2013). During all years except 2009, vaccination coverage was estimated to be between 0 and 2% of the cattle population. In 2009, 0.5 million doses were administered to cattle and coverage was estimated to be 11% of the cattle population. A recent study from Mexico has demonstrated that pre-exposure vaccination of cattle may be more efficient and economically beneficial than control efforts focused on depopulation of vampire bats (Anderson et al., 2012). However, even if rabies risk was removed from the equation, the secondary infections that commonly result from vampire bat depredation still poses a serious economic hardship for farmers in lost production value of affected herds (Flores-Crespo and Arellano-Sota, 1991).

Historically in Guatemala, livestock farming was most prolific in the southeastern region of the country. However, an increase in sugar cane and rubber production in the southeastern region has spurred significant land use conversion, and livestock farming and the associated burden of rabies has primarily shifted to the northwestern region of the country, though smaller dairy operations remain active in the southeast. While the number of rabies cases in dogs in Guatemala appears to be declining, the number of cases in cattle has been rising steadily over the past decade (OIE, 2013), though the impact of testing effort is unclear due to the absence of reported denominator data. As virus typing is not performed on positive cases, it has not been possible to link the rise in cattle cases with vampire bat rabies. However, this scenario is most likely given the strong association of vampire bats with cattle rabies outbreaks elsewhere throughout Latin America and the high number of cattle cases and rare occurrence of canine cases in some Departments (e.g., Petén, Alta Verapaz). Despite a lack of conclusive laboratory evidence linking rabies in cattle to bats, vampire bat control activities (i.e., poisoning or culling) are conducted in Guatemala in response to suspected outbreaks in cattle, although these are reactive strategies and sporadically applied. While they may eliminate local colonies of bats, and reduce bite incidence to cattle within a short time frame, these strategies are ineffective at controlling rabies virus circulation in vampire bats at a landscape scale. Thus, vaccination is necessary to protect livestock against rabies infection. During past suspected outbreaks, mass vaccination of cattle was initiated with assistance from the Ministry of Agriculture (MAGA), but suspect clinical cases of rabies in vaccinated cattle have raised concerns about the efficacy of the vaccines used – as reported elsewhere (Oliveira et al., 2000). There are several possibilities regarding such cases, including scenarios that animals are incubating the disease prior to vaccination, that the vaccine was improperly stored or administered, that the animal did not actually die of rabies (i.e., no lab confirmation of case), or potential for reversion of virulence of the modified live vaccine (Whetstone et al., 1984). One recent paper has highlighted the complexity of diagnosing rabies based on clinical signs in areas where other neurologic diseases of cattle can be present (Ramirez-Romero et al., 2014).

The objectives of this study were to understand factors associated with bat bites among cattle, to determine whether unvaccinated cattle had evidence of rabies virus exposure and evaluate whether exposure was related to bat bite prevalence, and to assess whether cattle demonstrate adequate seroconversion to commercial modified live rabies vaccines licensed in Mexico and used in Guatemala. This study compares both the short-term response to two different rabies vaccines and the maintenance of antibody titers over one year post vaccination.