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The protective effectiveness of an inactivated bovine ephemeral fever virus vaccine

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ABSTRACT

Bovine ephemeral fever (BEF) is an important viral disease of cattle. Despite the extensive use of inactivated vaccines for the prevention of BEF, a controlled study of their field effectiveness has never been performed. We conducted a large field effectiveness study of a BEF inactivated vaccine, during a large BEF outbreak. Neutralizing antibody titers measured in 385 heifers and calves 1 month after 2nd vaccination averaged 1:91.8 ($CI_{95\%}$ = 76.6–110). The effectiveness study enrolled 2780 cows in nine herds. In two herds cows vaccinated twice, 1 year before the outbreak and once 2–3 months before outbreak onset were compared with non-vaccinated cows. Average vaccine effectiveness of three vaccine doses compared to no vaccination was 47% ($CI_{95\%}$ = 34–57) in these herds. In two other herds cows vaccinated twice 1 year before the outbreak and twice again 2–3 months before outbreak were compared with cows vaccinated only twice 2–3 months prior to the outbreak. Average vaccine effectiveness of four doses compared to two doses was 49% ($CI_{95\%}$ = 25–65) in these herds. In five herds cows vaccinated twice 2–3 months before outbreak onset were compared with non-vaccinated cows. This vaccination schedule was shown to be non-effective (average effectiveness = 2%, $CI_{95\%}$ = −14–17). Milk production analysis on one of the effected herds, in which 56% vaccine effectiveness and an absolute reduction of 27% in morbidity were documented, revealed a net milk production loss of 175.9 kg/sick cow ($CI_{95\%}$ = 127.9–223.9) and an average gain of 37 kg for each vaccinated cow ($CI_{95\%}$ = −3.6–77.7). This study indicates that despite the fact that two vaccine doses of the tested inactivated vaccine elicited high titers of neutralizing antibodies, partial protection was induced only when at least 3 doses were administrated before natural challenge.

1. Introduction

Bovine ephemeral fever (BEF) is an economically important viral disease of cattle and buffalo which occurs mostly in tropical and subtropical climates in Africa, Asia, the Middle East and Australia (Walker, 2005). Both live attenuated and inactivated vaccines are available for field

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use, with the former shown to induce longer lasting immunity (Tzipory and Spradbrow, 1973, 1978; Vanselow et al., 1995) than inactivated vaccines (Aziz-Boaron et al., 2013; Della-Porta and Snowdon, 1979; Inaba et al., 1973). However, attenuated vaccines are considered less safe. Possible risks include adverse clinical signs (Della-Porta and Snowdon, 1977), reversion to virulence, especially due to relatively high mutation rate of RNA viruses (Nak-Hyung Lee et al., 2012), as well as introduction of other contaminating viruses during the preparation process (Pastoret, 2010; Studer et al., 2002).

To date the only controlled field effectiveness study conducted for BEF vaccines was performed in Australia for a live virus vaccine, partially inactivated after mixture with the adjuvant Quil A. (Vanselow et al., 1985, 1995). Administration of two doses of this vaccine resulted in high neutralizing antibody (NA) titers and 90% protective effectiveness, which lasted at least 12 months.

A MONTANIDE™ ISA 206 VG (water-in-oil-in-water) inactivated vaccine was developed in the Kimron veterinary institute in Israel (Aziz-Boaron et al., 2013). This vaccine was found to be safe and immunogenic, inducing a significant NA response (up to 1:256) following the second, third or fourth booster vaccination. However, a fast decline in NA titers was observed after 120 days (Aziz-Boaron et al., 2013). In addition, two out of 30 cows did not respond to vaccination and did not develop specific NA. This article describes the results of a large field study examining for the first time the effectiveness of various administration protocols of this inactivated vaccine.

2. Materials and methods

2.1. The vaccine

A MONTANIDE™ ISA 206 VG (water-in-oil-in-water) inactivated BEF virus (BEFV) vaccine was used in this study. BEFV isolated in Israel in 2000 (Yaqum-00) was used as the inactivated virus in this vaccine in a concentration of $10^{4.5}$–$10^{5.5}$ $TCID_{50}$/ml. Further details on the preparation, immunogenicity and safety of this vaccine were recently described (Aziz-Boaron et al., 2013). All animals were vaccinated intra-muscularly (IM).

2.2. Serum neutralization test

BEFV NA were detected in the collected sera using the serum neutralization (SN) test as was recently described (Aziz-Boaron et al., 2013).

2.3. Ethics

The study took place in several dairy herds of high-producing Israeli Holstein cows located in the southern Coastal Plain region in Israel with the owner's permission and cooperation. The study was approved by the Institutional Animal Care and Use Committee of the Ministry of Agriculture.

2.4. Study design

The study was divided to two stages. The first stage took place during the summer of 2007 aiming at monitoring the immune response following 1st and 2nd vaccination with the inactivated vaccine. In addition, it was aimed at revealing the percentage of cows not responding to vaccination in three different age groups. The studied population included 9 dairy herds located along the Jordan Valley, in which cattle bearing even numbers were vaccinated IM twice, 1 month apart with a 1 ml dose of vaccine. Cattle bearing non-even numbers were not vaccinated and served as a control group in order to monitor natural BEFV exposure during the study period. In each herd, blood samples were obtained from 10–15 vaccinated cows from three age groups: calves (6–12 months), pregnant heifers and primiparous heifers, according to the following schedule: before vaccination ($n = 401$), 1 month after 1st vaccination ($n = 382$) and 1 month after 2nd vaccination ($n = 385$). Blood samples were obtained from the non-vaccinated cattle ($n = 298$) 1 month after 2nd vaccination, parallel to the last sampling of the vaccinated cows. Sera were separated from whole blood and kept at −70 °C until the performance of SN assay. The average antibody titer following each vaccination was calculated for each age group in each of the three samplings. The distribution of the non-responding (NA titer = 1:1) and weak responsive (NA titer <1:8) cows according to age group was also analyzed.

The second stage was aimed at testing the effectiveness of the vaccine. The study population included cattle from 9 dairy herds located in the north and south of the Jordan Valley and the Jezreel Valley. In all herds, cattle were divided into two reference groups: Cows bearing an even number were referred to as the vaccine group and cows bearing an odd number were referred to as the reference group. Herds were vaccinated in several schedules. In some of the herds the reference group was vaccinated as well but always using a lower number of vaccine doses than the vaccine group. Vaccinated groups received two, three or four doses of 1 ml inactivated Israeli BEFV vaccine which was administrated IM during the summer (June-August) of 2007–2008 as follows: In **herds 1–5**, two vaccinations were administered to the vaccine group 1 month apart during 2008. In **herds 6–7**, two vaccinations were administered to the vaccine group, 1 month apart in 2007 and one vaccination in 2008. In Herds **8–9**, two vaccinations were administered to the vaccine group 1 month apart in 2007 and two vaccinations 1 month apart in 2008. In **herds 8–9**, reference group was also vaccinated with two vaccinations 1 month apart in parallel to the vaccine group during 2008. Approximately 2 months after the 2008 vaccination (during September-October) a BEF outbreak had occurred in Israel. Clinical information on individual cow morbidity was collected by the herdsmen on a daily basis in herds 1–9, both by visualization of cows and by monitoring milk production. Computerized daily milk production data were collected automatically at the milking parlors by the Afifarm™ software (Afikim, Israel) and saved to computer files by the herd management software Noa™ (Israel Cattle Breeders Association,