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## The long term effect of age and maternally derived antibodies against foot and mouth disease on the serological response following vaccination in young dairy calves

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## ABSTRACT

In Israel, occurrence of foot and mouth disease (FMD) in dairy farms is rare. However, when FMD outbreaks occur, dairy calves are the most affected, despite routine vaccination. Contradictory findings exist regarding the effect of age and maternally derived antibodies (MDA) on the serological response following vaccinations against FMD in dairy calves. Furthermore, the long term effect of FMD vaccination regimen during early life was rarely assessed. This study was conducted in order to assess both the short and long term effects. In total 44 non-vaccinated calves were divided into four groups of different age. Calves were vaccinated up to four times and 484 serum samples were collected on 11 time points in a period of 70 weeks. Virus neutralizing tests were performed in order to determine the neutralizing antibody titers (NAT) against the vaccine strains (homologous serotypes): O-4625, O-Manisa, ASIA-1-Shamir and the heterologous serotype A-Turkey-20/2006. A similar NAT pattern was observed to all serotypes and therefore statistical analysis was restricted to O-4625 serotype. The MDA titer was negatively associated with the age of the calves and the MDA half-life was 22 days. We demonstrated that early vaccination of calves (younger than three months) resulted in low NAT, even after four repeated vaccinations, compared with vaccination of calves older than three months. The percentage of time in which these calves had a NAT above 2.0 (log<sub>10</sub>) between the age of six months and 1.5 years was significantly lower compared to older calves (older than three months). Additionally, we found that by increasing the frequency of vaccination in calves older than three months, it is possible to reach high NAT by the age of one year. Adoption of such a vaccination regimen in Israel as well as other FMD endemic countries may allow better protection against FMD in dairy calves and reduction in FMD incidence.

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### 1. Introduction

Routine vaccination of livestock against foot and mouth disease (FMD) virus is recommended in countries with endemic infection [1]. Currently, most commercially available vaccines are based on inactivated FMD viruses with oil or aluminum and saponin based adjuvants [2].

In Israel, low endemicity of FMD exists among small ruminants [3]. In addition, repeated incursions of FMD viruses from surrounding countries [4,5] result in reoccurrence of FMD epidemics, despite the control measures applied against FMD. These include

mainly quarantines and emergency vaccination applied during outbreaks and routine annual vaccination of all livestock.

Vaccination schedule varies between different cattle production systems, yet, in general, calves are vaccinated twice by the age of six months. A detailed vaccination scheme by the Israeli Veterinary Services (IVS) is described in the supplementary (Supplementary Table).

Previously, the presence of calves younger than six months was found as a significant risk factor for FMD outbreak occurrence in beef herds [6]. A possible explanation for this finding is higher susceptibility of those calves to infection due to insufficient humoral immunity, which was suggested to be the result of only a moderate elevation of the antibody titer following a single vaccination. This may suggest that a more intensive vaccination regimen, which

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would be applied in early stages of life may elicit a pronounced neutralizing antibody titers (NAT) increase and hence a better protection at early age. However, vaccination of young calves, in the presence of maternally derived antibodies (MDA), might result in insufficient humoral response [7] though this is supported only by part of the previous studies on FMD vaccinations [8–10], and contradicted by others [11–13]. Additionally, to our knowledge the long term influence of such early vaccination on immunity was never examined. Therefore, a study was conducted, aimed at determining the association of age and MDA with the serological titers acquired by vaccination. Additionally, an intensive vaccination regimen aimed at acquiring an early protection against FMD was evaluated.

This study is a part of a vaccine immunogenicity study which included: (i) unvaccinated calves (presented here); and (ii) vaccinated heifers and cows (for which results are presented in a separate article [14]).

## 2. Materials and methods

### 2.1. Study design

#### 2.1.1. Study population

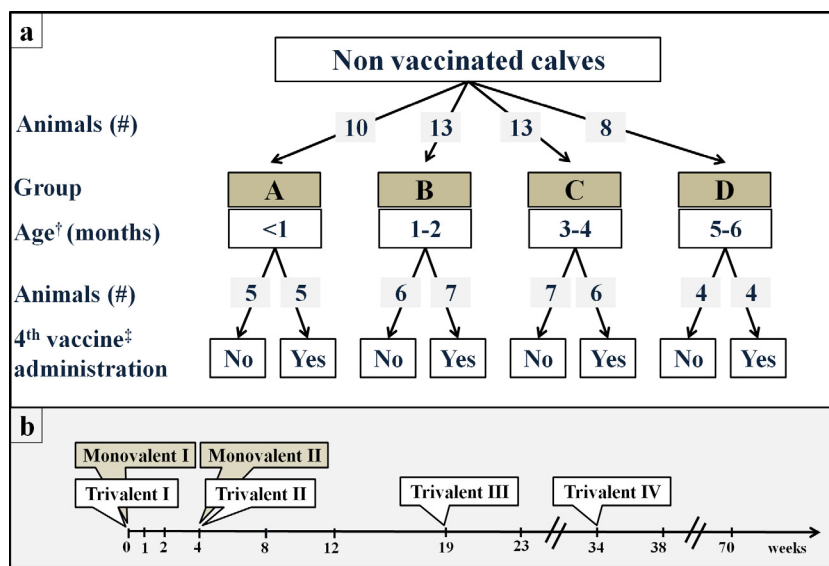
The study was conducted during July 2013 to December 2014 in a dairy farm (approximately 300 Israeli Holstein–Friesian milking cows) located in Kibbutz ‘Nezer Sireni’ (31.921571N, 34.827849E), at the center of Israel. The dairy farm was ‘closed’, i.e. heifers were locally bred and there was no introduction of animals into the farm. The study population included 44 non-vaccinated calves of varying ages, divided into four groups

(Fig. 1, Table 1). According to the OIE recommendations [1] groups of at least 5 calves should be used for estimation of vaccine efficacy. This study was conducted in a dairy farm and it was possible that animals will be removed from the herd during the study period, due to the farmer considerations (i.e. management and economic considerations). Therefore, the group size ranged between 8 and 13 calves.

Calves were selected from all female calves born (without intervention by the farmer) during the period between the end of January and end of July 2013. Calves that were the result of calving of twins (male and female) were excluded, as those are usually removed from the herd due to ‘Free-martin’ phenomenon. All calves were separated from their dams up to six hours after calving and bottle-fed (total volume of 4 l divided into two administrations) using a colostrum pool obtained from dams that were routinely vaccinated against FMD (at least 4 times). The calves in the study remained with their organic age groups throughout the study period.

#### 2.1.2. Vaccines

Calves were vaccinated three to four times during the study period: (i) at the beginning of the trial (week 0), (ii) after four weeks, (iii) after 19 weeks. Additionally, half of the calves were vaccinated for the 4th time after 34 weeks (Fig. 1). Selection of calves to be included in the 4th vaccine administration was based on the individual identification number and only odd numbers were vaccinated. Trivalent vaccines (O, A and Asia-1 serotypes) with more than 6PD<sub>50</sub> (i.e. the dose at which 50% of the cattle are protected) per dose were used (Aftopor™, Merial®, Pirbright, UK). The vaccine was prepared by the manufacturer with purified,



**Fig. 1.** Study design: (a) The number of calves in each group, the approximate age (†) of the group at the beginning of the study and the number of calves vaccinated with trivalent vaccine (‡) for the 4th time during the study period; (b) A scheme of the study timeline. Vaccine administration and sampling points (weeks) are indicated.

**Table 1**  
Characteristics of the groups participating in the study.

Group	N	Age at the beginning of the trial (days)		Approximate age of the group during vaccine administration (months)			
		Range	Average (SD)	1 <sup>st</sup>	2nd	3rd	4th
A	10	6–33	22.7 (10)	<1	<2	<7	<9.5
B	13	44–88	66 (14.3)	1–2	2–3	5–8	10.5–11.5
C	13	96–149	120.2 (14.7)	3–4	4–5	9–10	11.5–12.5
D	8	150–185	167.8 (12.3)	5–6	6–7	11–12	13.5–14.5

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