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The effect of maternally derived antibodies on the response of calves to vaccination against foot and mouth disease

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SUMMARY

Studies were carried out in South America to assess the effect of maternally derived antibody (MDA) on the responsiveness of calves to FMD vaccination. It was found that calves with MDA did not merely fail to respond to vaccination, but that their serum titres were depressed. This depression was proportional to the level of pre-existing MDA at the time of vaccination and following primary vaccination it persisted for a least 60 days. High MDA titres interfered with both primary and secondary responses. Animals with relatively low MDA titres were able to respond to vaccination, or at least to be sensitized so that on revaccination they showed a satisfactory response. The half-life of MDA was shown to be approximately 22 days, suggesting that under field conditions significant MDA titres are likely to persist for 4–5 months. A trial carried out in Brazil in which the primary course of two inoculations, 4 weeks apart, was initiated when the calves were 5–6 months of age, resulted in the reduction of FMD in the calf population from 11% to 0·9% over a 12-month period. The use of vaccination programmes of this type to lessen the incidence of FMD in young bovines is discussed.

INTRODUCTION

In areas of the world where foot and mouth disease (FMD) is controlled by regular vaccination, the incidence of disease is greatest in young stock under 2 years of age (Rweyemamu, Pay & Simms, 1982), suggesting that calves may not respond as well as adults to vaccination.

Two of the factors which may be responsible are the age of the animals and the presence of maternally derived antibodies (MDA). Previous results have shown, however, that in the absence of MDA the response of calves to FMD vaccination was not affected by the age of the animals (Nicholls *et al.* 1984). On the other hand there have been several reports suggesting that MDA are able to inhibit the calf's responses to vaccination against FMD (Graves, 1963; Srubar, 1966; van Bekkum, 1966; Wisniewsky & Jankowska, 1972; Prudovsky, 1973; Kruglikov *et al.* 1974; Uppal *et al.* 1975; Brun *et al.* 1977; Tekerlekov *et al.* 1980; Shankar & Uppal, 1982).

The present report describes a series of experiments carried out to examine (*a*) the effect of MDA on the primary and secondary vaccination responses of calves, (*b*) the rate of decay of these antibodies in the calf serum, and (*c*) how vaccination regimens could be modified to provide efficient protection of calves from FMD under field conditions.

MATERIALS AND METHODS

Vaccines

All vaccines used throughout this study were commercial stocks with aluminium hydroxide and saponin as adjuvant (Telling *et al.* 1972).

Titration of neutralizing antibodies

The sera were assayed for neutralizing antibodies against homologous vaccine virus strains in a microneutralization metabolic inhibition (colour) test (Martin & Chapman, 1961) using BHK cells as the virus indicator system. Virus neutralization was indicated by the ability of inoculated cell cultures to grow and convert the colour of the pH indicator in the medium (phenol red) from pink to yellow.

Results were expressed as the logarithm of the reciprocal of the highest dilution which neutralized virus. Tests were duplicated and the mean values for repeat tests calculated.

Experimental strategy

In order to demonstrate the effect of MDA on the calfhood responses it was desirable to vaccinate calves possessing a wide range of MDA titres. Thus, in the first experiment the calves derived from cows which had been vaccinated 10 days to 4 months before parturition were vaccinated when 1 week of age. In the second experiment the calves were of various ages from 1 to 4 months at the time of vaccination. Simultaneously, but in a separate experiment, the MDA decay rate ($t_{\frac{1}{2}}$) was determined. Finally this information was used to modify the vaccination programme employed on several ranches in Brazil. Using several thousand cattle, the incidence of FMD in calves was monitored when the pre-existing and modified vaccination schedules were employed.

Effect of MDA on the primary response of 1-week-old calves

In Uruguay 38 calves, born 10–129 days after vaccination of their dams, were bled and vaccinated when 1 week old. Twenty-one days later they were bled again and their sera were stored at −20 °C until examined for neutralizing antibodies.

A further six calves, kept in England, which were devoid of FMD-specific MDA, were also vaccinated when 1-week-old using the same batch of vaccine and bled on the day of vaccination and 21 days later.

Effect of MDA on the primary and secondary responses of calves of various ages

Fifty-nine calves, born from vaccinated dams in Brazil, were bled and vaccinated when 1–4 months old and bled again 30 days later. Some of the calves from each age group were revaccinated at day 30 after primary vaccination and all were bled again at day 60 (Table 1).

Table 1. *Design of experimentation on effect of MDA on primary and secondary response – Brazil*

Group	Calf age (months)	Subgroup	No. of animals	Vaccination Schedule Day 0	Day 30
1	1	1A	10	✓	✓
		1B	5	✓	—
2	2	2A	10	✓	✓
		2B	4	✓	—
3	3	3A	11	✓	✓
		3B	4	✓	—
4	4	4A	9	✓	✓
		4B	6	✓	—

Decay rate of maternally derived antibodies in calf serum

Eleven calves born from 4 to 6 months after the last vaccination of their dams were used. Blood samples were taken from calves on five occasions over a period of 4 months, during which time the calves' ages varied from 7 to 142 days.

Sera were stored at −20 °C until examined for neutralizing antibodies.

Protection of calves by vaccination under field conditions

A total of 53008 cattle on four ranches were vaccinated against FMD according to a 'traditional' South American vaccination schedule or according to a revised schedule, details as follows:

(*a*) *Traditional schedule.* All cattle were inoculated at 4-month intervals, irrespective of age. This group included half of the cattle on three ranches and all those on a fourth: 9056 calves were involved.

(*b*) *Revised schedule.* The adults were vaccinated at 4-month intervals but vaccination of the calves was delayed until they were 5–6 months old. The calves were also revaccinated 1 month later. This group was comprised of all the animals which remained unvaccinated on the three ranches mentioned in paragraph (*a*) above, and here 7951 calves were involved.

FMD was endemic in the area and the incidence of the disease was monitored in the ranches under study over a 12-month period.

RESULTS

Primary responses of 1-week-old calves

Calves devoid of MDA responded satisfactorily to vaccination and the mean antibody titres at 21 days post-vaccination for the O, A and C valencies were 2·1, 1·5 and 1·8 $\log_{10} SN_{50}$ respectively. In contrast, calves which had pre-existing maternal antibodies responded poorly (Fig. 1). The degree of suppression of post-vaccination response of these calves appeared to be related to MDA titres at the time of vaccination. It was, therefore, possible to construct a regression of post-vaccinal antibody increase/decrease against the level of MDA at the time of vaccination (Fig. 2). The linear regression produced a significant fit to the points ($P < 0{\cdot}01$) and their slopes were similar for each valency (Table 2).

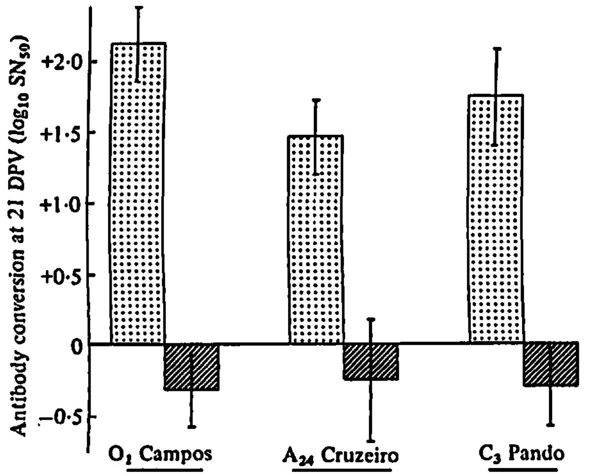

Fig. 1. The response of 1-week-old calves to FMD vaccination in the presence (▨) or absence (▦) of maternal antibody. The columns indicate the mean antibody titre of the groups and the vertical bars represent two standard deviations. DPV = days post vaccination.

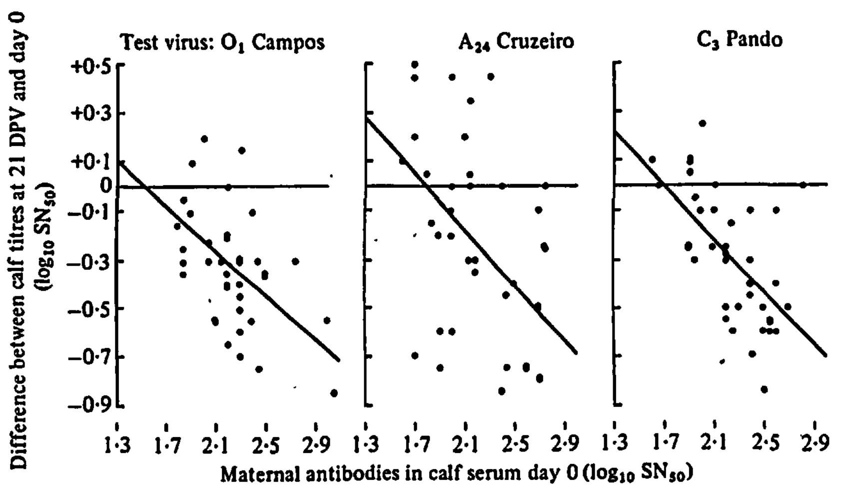

Fig. 2. Effect of maternal antibodies on primary response. DPV = days post vaccination.

Table 2. *The characteristics of the regression of antibody differential (i.e. day 21 to day 0 titres) on prevaccinal maternal antibody titre – Uruguay*

	21 days post-vaccination		
Virus valency	Correlation coefficient	S.E.	Slope
O_1 Campos	−0·58	0·31	−0·46
A_{24} Cruzeiro	−0·49	0·38	−0·58
C_3 Pando	−0·60	0·22	−0·54

P < 0·01 in all cases.

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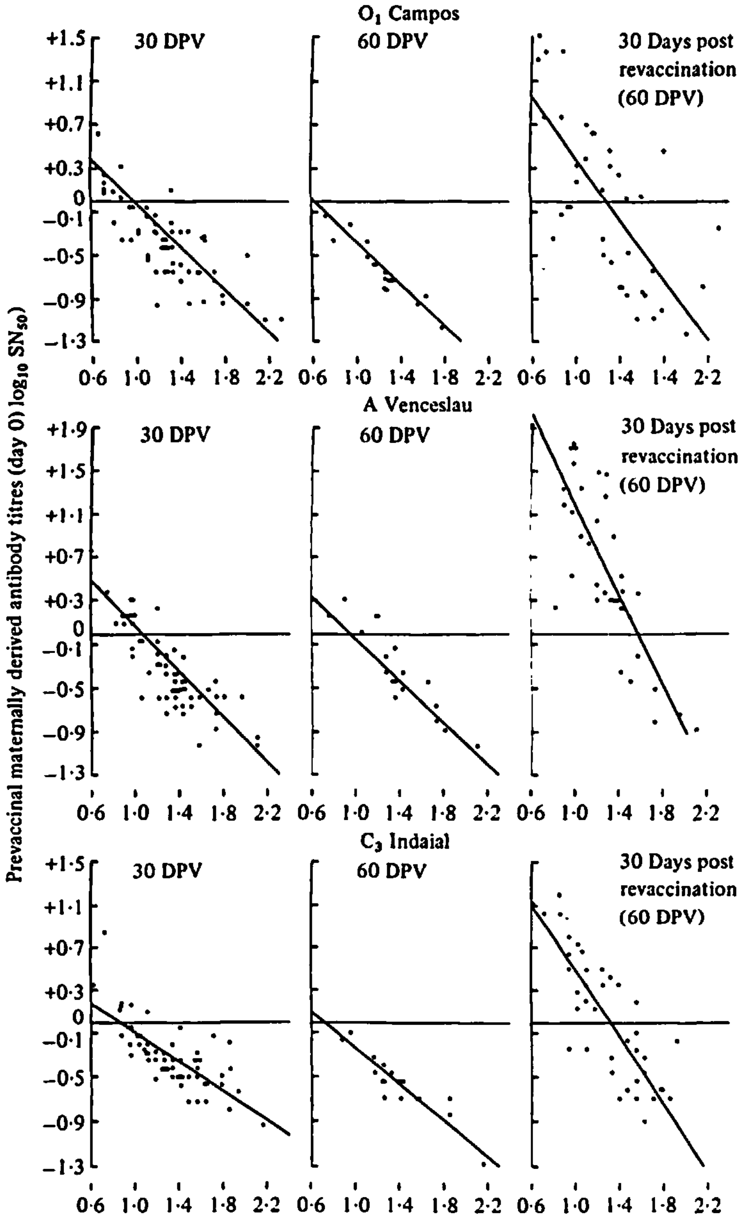

Fig. 3. Response of calves to primary and secondary vaccination in the presence of maternally derived antibody. DPV = days post vaccination.

It was noted that, in spite of the wide variation in the interval between vaccination of the dams and parturition in the first experiment, the serum titres of the calves at 1 week of age fell within a narrow range (1·6–2·8 $\log_{10}SN_{50}$ for > 97 % of calves).

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Table 3. *The characteristics of the regression of antibody differential (i.e. post-prevaccinal titres) on prevaccinal maternal antibody titre – Brazil*

	Primary Response						Secondary Response		
	Day 30			Day 60			Day 60		
Virus valency	*r*	S.E.	Slope	*r*	S.E.	Slope	*r*	S.E.	Slope
O_1 Campos	−0·77	0·28	−1·02	−0·90	0·16	−1·00	−0·71	0·54	−1·40
A Venceslau	−0·84	0·21	−0·98	−0·90	0·17	−1·10	−0·83	0·45	−2·10
C_3 Indaial	−0·75	0·20	−0·68	−0·90	0·11	−0·82	−0·85	0·37	−1·60

$P < 0.01$ in all cases. *r* denotes correlation coefficient. S.E. denotes standard error.

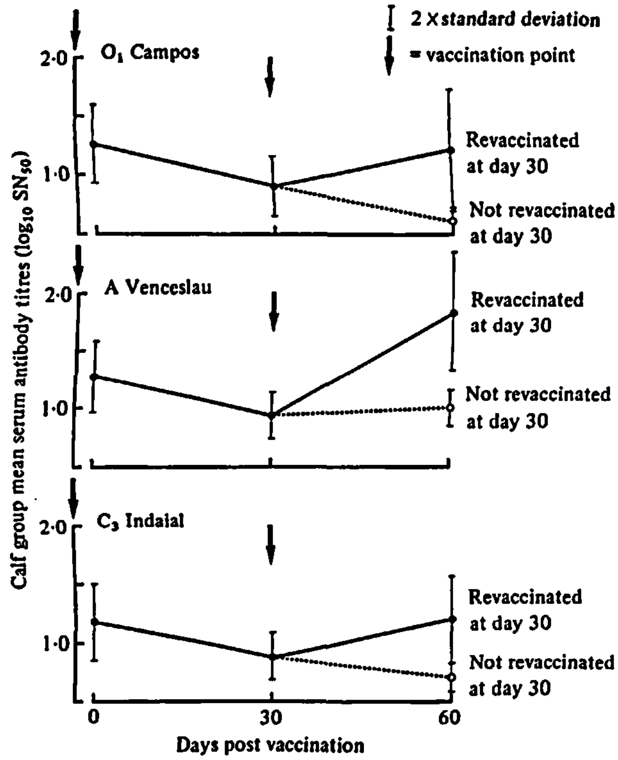

Fig. 4. The response of calves to FMD vaccination in the presence of maternal antibody.

Primary and secondary responses with calves aged from 1 to 4 months at the time of vaccination

These calves showed a wide range in their MDA titres (0·5–2·3 $\log_{10}SN_{50}$) at the time of first vaccination. It was again possible to construct regressions of the post-vaccinal increase/decrease of serum antibody titres against the level of maternally derived antibodies at day 0 for both primary and secondary responses (Fig. 3) and these regressions again showed a significant fit of the lines to the points ($P < 0.01$) in each case (Table 3).

The group mean titres of the calves at 30 days after primary vaccination were lower than those observed initially (prior to vaccination). When no additional

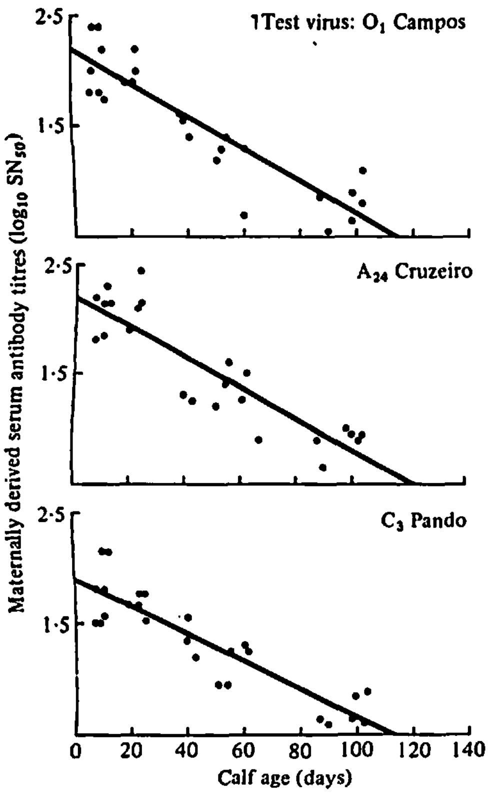

Fig. 5. Decline of maternally derived antibodies with time.

vaccination was given at day 30 these levels declined still further by day 60. On the other hand when revaccination was given at day 30 an increase in mean titres was provoked by day 60 although there was considerable animal to animal variation in this response (Fig. 4).

Decay rate of maternally derived antibodies in calf serum

Two of the calves had barely detectable levels of maternally derived antibodies in their serum at the earliest sampling, despite receiving colostrum during the first 36 h of life and were therefore excluded from further analysis. The results from calves older than 103 days were also excluded as by that time the antibodies had generally reached their lowest measurable value. Linear regression of $\log_{10}SN_{50}$ values against time calculated from the data (Fig. 5) had a significant fit ($P < 0{\cdot}01$) to the points for each virus valency and indicated a half-life of 22·2 days.

Protection of calves under field conditions

Of the 9065 calves vaccinated at 4-month intervals irrespective of age ('traditional' schedule), 1007 (11%) contracted FMD, whereas of the 7951 which were subjected to the revised schedule (vaccination delayed until the calves were 5–6 months old and repeated 1 month later) only 73 (0·9%) developed lesions. The results of a 2 × 2 contingency analysis ($\chi^2 = 741$) suggests that the difference in the number of infected animals in the two groups was unlikely to be due to chance

($P < 0{\cdot}01$), assuming that the possibility of an FMD outbreak was equal in all vaccination groups.

Adult cattle which had received multiple vaccinations according to the 'traditional' programme were almost all protected from infection even when their calves were affected by FMD.

DISCUSSION

The effect of MDA on the response of calves was investigated initially in Uruguay. Here, the age of calves was standardized, as 1 week old at time of vaccination, and it was hoped to produce a range of MDA titres by selecting animals born at various intervals after vaccination of their dams. In this manner it was hoped to avoid confusing the effect of varying calf age with the effect of MDA. In the event, however, the calves did not have a wide range of MDA levels and all the titres, except one, ranged between 1·6 and 2·8 $\log_{10} SN_{50}$ on the day of vaccination. It was not possible, therefore, to compare the effect of low with high levels of MDA but despite this limitation, it was still possible to demonstrate that the MDA depressed the response to vaccination in a linear fashion. This could not be ascribed to poor potency of the vaccine employed since the same vaccine batch provoked a satisfactory immune response in British calves which were devoid of specific MDA against foot and mouth disease. The decline in the antibody titres observed at 21 days after vaccination was probably due, to some extent, to natural decay of the MDA. If vaccination had not been carried out the serum titre would be expected to have dropped by approximately 0·3 $\log_{10}$ during the three week observation period. In fact, the titres of many of the vaccinated animals were depressed far more than that. The results shown in Fig. 2 and 3 indicate that depression of titres by 0·3 to 1·0 $\log_{10}$ were common, suggesting that vaccination of the young calves was not only ineffective in promoting any improvement in the antibody titres but also led to a strong depressive effect on the MDA titres which existed at the time of vaccination.

The relatively small range obtained in the MDA titres in the first experiment has already been noted. In the second experiment a much wider range of MDA was observed and here the responses were again inversely proportional to the level of pre-existing antibody. The standard error on the regression lines was less than in the first experiment and the coefficient of correlation was correspondingly higher. The depressive effect persisted for at least 60 days after vaccination and could not therefore be considered transient.

The responses to secondary vaccination were more variable than primary responses. This was not unexpected as at the time of revaccination the MDA titres in some calves were still high; in others the MDA titres had waned to low levels and yet others, which had responded to primary vaccination, were capable of true anamnestic response. In spite of this, however, the titres provoked by revaccination would be regarded as protective in the majority of calves.

It was observed that depression of secondary responses was related in a linear fashion to the MDA titres at the time of primary vaccination just as was the depression of the primary responses but the regression slopes were steeper in the former case.

The level of response attained in the presence of maternal antibody varied from one trial to another. In Uruguay, for example, calves with MDA titres as high as 2·3 $\log_{10}$ responded to vaccination, albeit at a depressed level, whereas calves in Brazil failed to respond in the presence of MDA titres higher than 1·3 $\log_{10}$. It seems likely that such differences in the responses were governed by the potency of the vaccines employed.

Muntiu *et al.* (1969) reported that 1-month-old calves required vaccine 16 times more potent than that given to adult cattle in order to provoke similar levels of response. This is difficult to reconcile with the results reported here, especially as it was claimed that the cattle were derived from a region of Rumania free from FMD for 10 years and the calves were born of mothers which had not been vaccinated against FMD. MDA were not likely to have been present in these calves. Other factors may have been important since the authors also reported that cattle as old as 6 and 12 months did not respond as well as older cattle to FMD vaccination. Several non-specific variables which influence responses have been identified, including intercurrent disease (Scott *et al.* 1977), genetic factors (Eissner, Uhlmann & Lorenz, 1972) and geographical location (Sutmoller & Vieira, 1980). The extent to which these factors affect calfhood responses has not been fully evaluated but their effects could explain the differences between our results and those obtained by Muntiu and his colleagues. Further investigations are indicated in order to clarify these discrepancies.

With regard to improving the calfhood responses several workers have suggested that oil emulsion vaccines give better responses than aqueous vaccines in cattle (Cunliffe & Graves, 1963; Adler, Murillo & Rivenson, 1966; Rivenson, 1972; Auge de Mello & Gomes, 1977) but experiments to demonstrate their effect in calves in the face of MDA (Brun *et al.* 1977) have been inconclusive.

The natural route of infection of cattle with FMD virus is via the upper respiratory tract (Hyslop, 1965; Eskildsen, 1969; Sellers, 1971). In other upper respiratory tract viral diseases (for example, infectious bovine rhinotracheitis) it is common practice to administer a live vaccine intranasally. The rationale for this is to provoke mucosal antibody and interferon as first line of defence (Todd, 1973). Although FMD convalescent cattle develop secretory IgA response, neutralizing antibody in the pharynx following vaccination seems to be a result of transudation rather than local secretion (Francis, Ouldridge & Black, 1983) and would therefore be expected to be limited by the presence of MDA as discussed above.

It is not practical to investigate the possibility of intranasal vaccination with live FMD vaccines since such vaccines carry with them the hazard of reversion to virulence and Venezuela is at present the sole country in which they are permitted (Mowat, Garland & Spier, 1978; Henderson, 1978; Casas Olascoaga, 1978; Rweyemamu, Pay & Simms, 1982).

Another approach would be to delay vaccination of calves until their MDA titres have waned. This requires a knowledge of their decay rate. The rate of decay of various classes of immunoglobulins available to the calf from the dam are known to differ from one another (La Motte, 1977; Sasaki, Davis & Larson, 1977; Ishikawa & Konishi, 1982). Any factor which alters the relative quantities of these immunoglobulin classes in the calf serum, such as the vaccination schedule of the dam, the interval between dam vaccination and parturition and the rate of absorption of the different immunoglobulin classes by the calf from the colostrum, is likely to alter the decay rate of antibodies in the calf serum. In the experiment described above MDA was shown to have a half life of 22·2 days. This value is comparable to that reported by Sasaki *et al.* (1977) for the rate of decay of IgG in bovines. A similar half-life value for maternally derived antibodies against FMD was reported by van Bekkum (1966) and also for antibodies against IBR and BVD by Brar *et al.* (1978). On the other hand, this rate of decay is at variance with that reported by Graves (1963), Glushko (1964) and Shankar & Uppal (1981).

Such an approach was adopted in the field trial carried out on several ranches in Brazil. In this case the initial vaccination was delayed until the calves were 5–6 months of age, followed by a second inoculation 30 days later to complete the primary vaccination course (Rweyemamu *et al.* 1982). This programme resulted in a substantial decrease in the incidence of clinical FMD on the ranches. It should also be noted that this regimen hardly interfered with the 4-monthly vaccination programme. It simply involved vaccinating calves 1 month before or after the main campaign. This level of extra animal handling was found to be cost beneficial to the ranch owners.

Although MDA persisted for approximately 4 months in case of the vaccine employed for experimental purposes (Fig. 5), the calfhood vaccinations in the revised field schedule were delayed until the animals were 5–6 months old. This extra delay was considered desirable because MDA, even with low and scarcely demonstrable titres, appeared capable of interfering with the calves' vaccination responses. Fig. 3 for instance shows that even when MDA with titres less than 1 $\log_{10} SN_{50}$ were present at time of vaccination the responses provoked added no more than 0·4 $\log_{10} SN_{50}$ to the titres during the following 21 days. (A potent vaccine was used which provoked titres of 1·5–2·2 $\log_{10} SN_{50}$ in calves which were devoid of MDA. See Fig. 1.)

A further reason for delaying vaccination until the calves were 5–6 months old was that the persistence of MDA is dependent on both their decay rate and their initial titres in the calves. Hence although MDA persistence of 115–120 days was demonstrated experimentally (Fig. 5), this could have been either longer or shorter according to whether the calves' initial titres were higher or lower. The factors influencing this (vaccination response of the dam, potency of the vaccine employed, interval between vaccination of the dam and parturition) have been discussed elsewhere (Nicholls, 1983).

This type of programme is ideally suited to situations where a seasonal incidence of FMD occurs. Under such conditions the calving season and vaccination programmes can be organized so that calves receive their primary course of vaccinations prior to the season of high disease risk. However, the data presented here suggests that a proportion of young calves would be susceptible to infection either on account of their having absorbed less than optimal levels of colostral antibody or because of declining MDA levels. Furthermore, a single vaccination in the presence of high MDA titres appears capable of suppressing these levels and thereby, presumably, increasing the risk of infection. In circumstances where a region or farm is immediately threatened by a neighbouring disease outbreak it seems reasonable to suggest that, for additional support to such a vaccination programme, all calves regardless of age be vaccinated twice, 2–4 weeks apart, in order to ensure antibody response in the majority of cases.

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