Reactions to heartwater vaccination in crossbred Zebu cattle

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ABSTRACT

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One thousand and ninety-four crossbred Zebu cattle were immunized against heartwater with a sheep-blood vaccine containing the Ball 3 strain of *Cowdria ruminantium*. Animals experiencing febrile reactions were treated at various stages of the reaction with tetracycline. Four hundred and sixty-two (42,2%) reacted, six (0,6%) of which died. Deaths were significantly less frequent in cattle treated on the first day of reaction (2/323, 0,6%) than those treated at a later stage (4/61, 6,6%). The mean incubation period was 15,6 d (range 7–23 d). Incubation period and frequency of reactions varied significantly between farms, between vaccine batches and between vaccine doses. Variations in frequency of reactions, incubation period and severity of reaction did not affect the efficacy of immunization, as assessed by seroconversion.

Keywords: Author, author

INTRODUCTION

Heartwater (*Cowdria ruminantium* infection) was first recognized as an important disease of domestic ruminants during the 19th century in South Africa and is now known to be widespread throughout sub-Saharan Africa (Provost & Bezuidenhout 1987). Prevention of the disease depended entirely on control of the vector ticks, *Amblyomma* spp., until the 1940s, when Neitz & Alexander (1941; 1945) developed a method of immunization involving the inoculation of infected sheep blood and treatment of the ensuing disease process, where necessary, with sulphonamides or, more recently, tetracyclines.

In South Africa, the majority of cattle experience febrile reactions after vaccination (Bezuidenhout 1989). In animals over the age of one month, such reactions are often fatal if they are not treated (Neitz & Alexander 1941). The optimal regimen for controlling reactions is to vaccinate the animals in small groups and to record rectal temperatures daily from 7–28 d after vaccination (Bezuidenhout 1989). Cattle showing an early morning temperature above 39,5 °C are treated on the first or second day that the temperature is elevated. Even under such careful supervision, however, some mortality is to be expected, which may occasionally reach 5% in adult animals (Barnard 1953; Sutton 1960).

The implementation of such intensive monitoring is, at best, time consuming and, at worst, impossible. Methods for block treatment on a set day during the period of reaction, have been devised in an attempt to circumvent daily monitoring (Du Plessis & Malan 1987; Bezuidenhout 1989), but because the incubation period is so variable, they increase the risk of mortality.

In Malawi, the need to immunize improved cattle against heartwater in support of immunization against East Coast fever (*Theileria parva* infection), anaplasmosis and babesiosis was demonstrated by Radley (1985) and Musisi, Quiroga, Ngulube & Kanhai (1989).

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Immunization against heartwater was introduced on a limited scale in 1989 on government farms in the East Coast fever endemic area, but widespread application has been inhibited by the need for intensive monitoring, which is impossible to provide in some circumstances. Attempts to develop regimens to control reactions by treatment with slow-release doxycycline implants or long-acting tetracycline at the time of vaccination or during the incubation period, have failed (Lawrence, Tjornehoj, Whiteland & Kafuwa 1993a; Lawrence, Tjornehoj, Whiteland & Kafuwa, in press).

As there appears to be no safe alternative to daily monitoring, data on vaccination reactions in improved cattle in Malawi have been analysed to characterize the timing and nature of the reactions, with a view to rationalizing and simplifying surveillance and treatment procedures.

MATERIALS AND METHODS

Cattle

Reactions were studied after heartwater vaccination in 1094 cattle in 44 groups, between 1989 and 1993. The cattle were mostly half to three-quarter crossbreds, predominantly Friesian X Malawi Zebu, with a substantial number of Brahman X Malawi Zebu and a few crosses with some other European breeds. They were aged between 6 to 36 months, except for one group of 4 weeks old. They were located on eight different farms in the central and northern regions, where heartwater is endemic. The farms are situated at varying altitudes, with different soil and vegetation types, different climates and different systems of management. Group sizes varied from 3–85; 17 groups, totalling 817 head, represented routine vaccinations, while 27 groups, totalling 277 head, were involved in experiments testing and evaluating vaccines.

Vaccine

The cattle were all vaccinated intravenously with a sheep-blood vaccine containing the Ball 3 strain of *C. ruminantium*. One batch of vaccine (RSA) was obtained from the Veterinary Research Institute, Onderstepoort, South Africa, and three other batches (HW002, HW004, HW006) were prepared in Malawi by conventional methods (Bezuidenhout 1989). The vaccines were stored and transported to the farms in liquid nitrogen and were thawed immediately before use. The dose varied from 0,2–5,0 mℓ, with a mean of 3,1 mℓ. The 50 % infectious dose (ID50) for cattle was established by titration for two batches (HW004, HW006) as 0,40 mℓ, and seroconversion was used as the indicator of infection (Lawrence, Whiteland, Malika & Kafuwa 1993b). Immediate anaphylactic reactions to vaccination were treated when they occurred with adrenalin 1:1 000, 1 mℓ intramuscularly (i.m.).

Monitoring and treatment

Cattle were monitored by recording rectal temperatures early in the morning every day during the expected period of immunization reaction. The periods of monitoring varied from group to group, depending on previous experience and prevailing circumstances, but all fell within the range of 7–25 d post-vaccination. Cattle showing early morning temperatures above 39,5 °C were considered to be reacting to vaccination and were normally treated with long-acting tetracycline (20 mg/kg i.m.) once or with short-acting tetracycline (10 mg/kg/day i.m.) for 3 d, although there were some departures from this regimen. Various brands of tetracycline were used. Seventy per cent of reactors were treated for the first time on the first day of reaction, 13 % were treated at some other stage or were not treated at all, and in the remaining 17 % the animals were found to be reacting on the first day of monitoring and the time of treatment in relation to reaction could not be established.

Serology

In experimental studies on three farms, sera collected at the time of vaccination and approximately 42 d later, were tested at 1/30 for antibodies to *C. ruminantium* by indirect immunofluorescence using an endothelial cell-culture antigen (Lawrence *et al.* 1993b).

RESULTS

Frequency and time of reaction

Four hundred and sixty-two cattle (42,2 %) reacted to vaccination and six (0,6 %) died. Reactions started between day 7 and day 23 after vaccination (Fig. 1) with a mean incubation period of 15,6 d (SD ± 2,75).

The frequency of reactions and the time of reaction (before or after day 16) varied significantly between groups of cattle (χ^2 = 373,2, 84 d.f., P < 0,1, excluding groups of less than five animals). Variations in frequency and time of reaction were attributable to differences between farms, between vaccine batches and between vaccine doses. No differences were seen between ages or breeds of cattle, but data were limited, as many groups were excluded from the analysis of these factors owing to incomplete records.

Farms

A total of 856 cattle on all eight farms were vaccinated with RSA vaccine at doses of 2–5 mℓ. The frequency of reactions varied from 8,6–91,5 % (Fig. 2) and the difference was statistically significant (χ^2 = 106,80, 7 d.f., P < 0,1). The proportion of reactions which started before day 16 also differed significantly between farms (χ^2 = 49,16, 7 d.f., P < 0,1) and was positively correlated with the proportion of animals reacting (r =

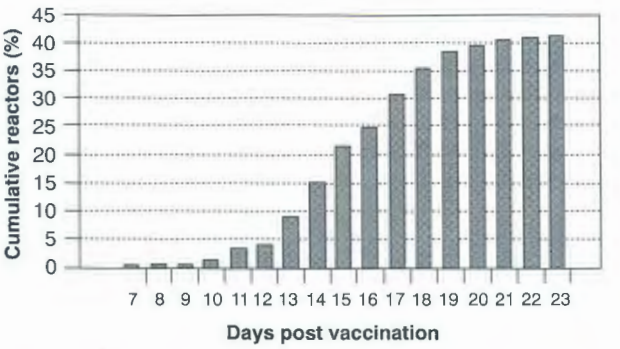

FIG. 1 Time of onset of febrile reaction after heartwater vaccination in 1094 cattle

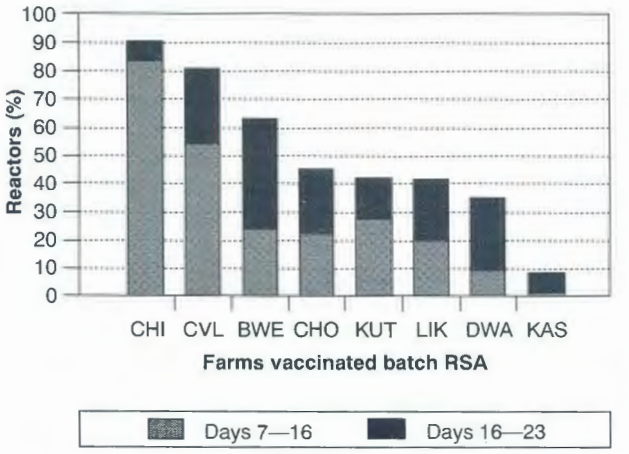

FIG. 2 Incidence and time of onset of febrile reaction in cattle on eight farms after heartwater vaccination

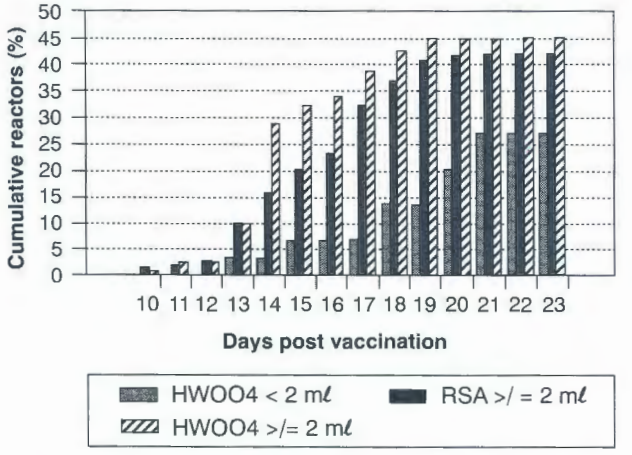

FIG. 3 Incidence and time of onset of febrile reaction on cattle on a single farm after vaccination with different batches and doses of heartwater vaccine

0,8414, 6 d.f., P < 1,0). There was no statistically significant correlation in six groups of cattle on five farms between the proportion of cattle reacting with temperatures above 39,5 °C and the normal temperature of the cattle, calculated from mean rectal temperature over the 3 d of monitoring before any reactions were recorded (r = 0,7176, 4 d.f., P > 10). Mean normal temperatures ranged from 38,0–38,8 °C.

Vaccine batches

On a single farm, 413 cattle were vaccinated with either RSA or HW004 vaccine at doses of 2–5 mℓ. HW004 provoked an earlier reaction than RSA. There was a significant difference between vaccines in respect of the proportion of animals reacting before 16 d (χ^2 = 8,58, 1 d.f., P < 1,0), but not in respect of the proportion of animals reacting by day 23 (χ^2 = 0,37, 1 d.f., P > 10) (Fig. 3).

Vaccine doses

On the same farm, 141 cattle were vaccinated with HW004 vaccine at doses between 0,2 mℓ and 5,0 mℓ. Cattle receiving less than 2 mℓ reacted significantly later (after day 16) than those receiving 2–5 mℓ doses (χ^2 = 4,82, 1 d.f., Yates correction applied, P < 5,0), but the apparent difference in the proportion of animals reacting by day 23 was not statistically significant (χ^2 = 3,29, 1 d.f., 10 > P > 5) (Fig. 3).

Seroconversion

Of 490 cattle tested before vaccine experiments were started on three farms, only four were positive to *C. ruminantium* at 1/30. Forty-eight unvaccinated controls in the experiments were tested after 6 weeks and only two were positive. The mean seroconversion rate after 6 weeks in 234 vaccinated cattle in 25 groups included in the study was 78,2%. There was no correlation between the time of reaction or the frequency of reactions in the group and the proportion of animals seroconverting (r = 0,084; 0,161, respectively, 23 d.f., P > 10).

Fatal reactions

Six of the 462 reactors died (Table 1). Two were treated on the first day that the temperature exceeded 39,5 °C and two on the second day; one was not treated and died on the second day and one evaded the monitoring procedure and was detected and treated *in extremis* only. In all, 2/323 (0,6%) animals that were treated on the first day died, as compared to 4/61 (6,6 %) in which treatment was delayed, and the difference was significant (χ^2 = 8,285, 1 d.f., Yates correction applied, P < 1,0). On one farm, where treatment was delayed deliberately until after the first day, there was an apparent difference in mortality amongst reactors in calves 6–9 months old (3/12) and calves 4 weeks old (0/11), but the difference was not statistically significant (χ^2 = 1,492, 1 d.f., Yates correction applied, P > 10).

Severity of reaction

There were no significant correlations between peak temperature during the reaction in surviving reactors

TABLE 1 Fatal heartwater vaccination reactions in cattle vaccinated with RSA vaccine

Temperature/days post vaccination										
Tag no.	Farm	Dose	12	13	14	15	16	17	18	19
442*	LIK	5 mℓ	----------Not monitored----------							39,8 TD+
823	BWE	5 mℓ	38,0	39,2	39,0	39,6	40,0 T	40,0 T	38,6 TD	
833	BWE	5 mℓ	38,5	39,2	38,4	38,8	39,0	40,7	40,0 TD	
1219	BWE	5 mℓ	39,5	39,5	39,0	39,0	40,1	D		
1490	LIK	2 mℓ	38,4	38,0	38,5	38,3	38,6	38,4	38,9	40,7 TD
5109	DWA	5 mℓ	38,7	38,3	39,2	39,4	40,0 T	38,4 D		

* Tag lost, not monitored, treated *in extremis*
\+ T = treated tetracycline
D = died

and age of animal, incubation period, seroconversion or proportion of animals reacting in the group.

Recurrent reactions

Fifty-eight of 456 (12,7%) surviving reactors underwent a second febrile reaction, in which the temperature rose above 39,5 °C after it had fallen to 39,5 °C or below for at least 1 d following the initial reaction, and four of these had a third reaction. The mean time from the beginning of the first reaction to that of the second reaction was 4,4 d (range 2–9 d). Animals that were not treated for the primary reaction had a significantly greater chance of a second reaction (14/46, 28,3 %) than they would have had if treated at any stage (44/410, 10,7%) (χ^2 = 14,46, 1 d.f., P < 0,1). Recurrence of reaction was not related to the severity of the primary reaction, nor to the variety of tetracycline used to treat it. Recurrent reactions were not significantly less severe than primary reactions as judged by the degree of rise in temperature.

Continuous reactions

Fourteen of 456 (3,1%) surviving reactors experienced primary reactions continuing for more than 3 d, despite treatment. There were no significant correlations with the day of treatment or the drug used.

DISCUSSION

The reactions to heartwater vaccination in crossbred Zebu cattle were very similar to those recorded in 2743 cattle of various breeds in South Africa by Van der Merwe (1979), the most striking difference being in the proportion of animals which did not react with temperatures above 39,5 °C (57,8% in Malawi, 0,3% in South Africa). Continuous or recurrent (twin peak) reactions were also less frequent. However, the vaccine dose used in South Africa was much higher than that used in Malawi, as the cattle routinely received two doses of 5–10 mℓ vaccine at intervals of 5–7 d.

The analysis of reactions confirms the opinions of Van der Merwe (1979), Du Plessis & Malan (1987) and Bezuidenhout (1989) that the optimal regimen for control of vaccine reactions is daily monitoring and treatment. The monitoring period must be prolonged, as the time of onset of reaction is very variable, ranging in this study from day 7 to day 23 post vaccination. The very wide range of incubation periods and the frequency of recurrent reactions precludes any form of successful block treatment.

On the basis of the findings of this study, it is recommended that cattle be treated on the first day that the temperature rises above 39,5 °C. In those cattle in which treatment was delayed, the risk of death was increased tenfold. There was no evidence from this study to indicate that the immune response, as judged by seroconversion, would be improved by allowing the reaction to continue, although the situation may be different in sheep and goats (Du Plessis & Malan 1987). While it is recognized that the indirect immunofluorescence test for *C. ruminantium* is not specific (Du Plessis, Bezuidenhout, Brett, Camus, Jongejan, Mahan & Martinez 1993), there was no evidence in this study that non-specific reactions invalidated the test as an indicator of a specific immune response. Seroconversion after immunization has been shown to be correlated with the development of protective immunity in this type of cattle (Lawrence *et al.*, in press). Some animals recovered from an initial febrile reaction without receiving treatment, but in this study such animals were three times more likely to undergo a second reaction than those that were treated, and the second reaction was no less severe than the first. Conscientious monitoring and early treatment should limit

mortality during immunization to less than 1 %, as reported also by Van der Merwe (1979). It should be remembered that febrile reactions after heartwater vaccination may be caused by agents other than *C. ruminantium* (Uilenberg 1971). Some animals may be treated unnecessarily for non-specific transient febrile conditions. Others may fail to respond to tetracycline treatment and, if so, they should be examined for intercurrent infections and treated appropriately.

A wide variation in reaction to vaccination was found between groups of cattle, in respect of both time and frequency of reactions, but it bore no relationship to the immune response, as judged by seroconversion. The greatest variation occurred between farms, for reasons which were not established. They may have included genetic factors, and in this respect it is worth noting that crossbred Zebu cattle in Malawi are in general less than half as likely to react to vaccination as non-Zebu cattle in South Africa (Bezuidenhout 1989). Other possibilities are nutritional factors, management factors and monitoring procedures. In particular, where cattle are fractious, handling facilities are poor and temperatures are taken late in the morning when ambient temperatures are high, it might be expected that a higher proportion of animals would reach the critical temperature of 39,5 °C than would in normal circumstances. However, there was no evidence in the present study that differences in monitoring procedures were responsible for the variation that was seen.

Variations between doses and batches of vaccine were seen in respect of the incubation period, which was probably an indication of variations in the infectivity of the vaccine (Bezuidenhout 1989). However, the incubation period also became shorter as the susceptibility of the cattle to react to the vaccine increased.

There were indications on one farm that the frequency of reactions was lowest during the period April to June and highest during the period July to September, although it was not possible to exclude factors other than season as being implicated in the variation. Seasonal variation in susceptibility to the vaccine, if it were confirmed, could possibly be associated with seasonal variation in nutritional status or in serum conglutinin levels (Du Plessis, personal communication).

While overall variation between cattle groups was very wide in this study, it is probable that when vaccination is practised routinely on a particular farm, in similar groups of cattle at the same time of year, with a standardized vaccine, variation would be greatly reduced. It might then become possible to predict the timing, incidence and nature of the reactions with reasonable accuracy and even to modify the surveillance procedure to suit the local situation.

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