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# Control of Induced Infestations of Three African Multihost Tick Species with Sustained-Release Ivermectin

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ABSTRACT

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The efficacy of ivermectin, released intraruminally from a 28-day-delivery device was evaluated in two titration studies against induced infestations of adult *Rhipicephalus appendiculatus, R. evertsi* and *Hyalomma truncatum* on cattle. Cattle were given a sufficient number of devices to release ivermectin at approximately 20, 40, 60 or 80 $\mu$g kg$^{-1}$ day$^{-1}$ at a steady-state rate 7—28 days after administration. Tick mortality was recorded, engorged female ticks were weighed and individually incubated, and reproductive data were recorded to determine a reproductive index for the species at various dose levels. Mortality of male and female ticks compared to that of controls was directly related to the daily dose of ivermectin, as was the number of ticks not engorging. Ticks fed on ivermectin-treated cattle had a smaller mass when engorged and laid smaller egg-masses, both absolutely and as a proportion of engorged mass.

The index of reproduction of *R. appendiculatus* was reduced by more than 99.9% at 20 $\mu$g kg$^{-1}$ day$^{-1}$, and the reproductive indices of *R. evertsi* and *H. truncatum* were reduced by more than 99.9% at dose rates of 40 $\mu$g kg$^{-1}$ day$^{-1}$ and above.

Practical implications of the application of sustained-release ivermectin for the control of multihost ticks and tick-borne diseases are discussed.

## INTRODUCTION

Control of ticks and tick-borne diseases is of great importance to the livestock industry in Africa. Control of the brown ear tick, *Rhipicephalus appendiculatus*, is especially important because it is the vector of *Theileria parva*, the causative organism of East Coast Fever. Control of other *Rhipicephalus, Hyalomma, Amblyomma* and *Boophilus* spp. is equally important in many areas.

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The conventional method of controlling tick infestation is through the regular topical use of acaricides (dipping, spraying or hand-dressing). These methods are labour-intensive and time-consuming, and may be ineffective if not regularly and correctly applied. Administration of a systemically active compound in a sustained-release formulation is a possible alternative method of tick control.

Ivermectin is active against a wide range of internal and external parasites, including some tick species, at extremely low dosages (Campbell and Benz, 1984). The dose required is low enough to make it an excellent candidate for systemic tick control by administration by means of a controlled-release device.

Minimum effective daily dosages of ivermectin for several species of ticks, including *Amblyomma americanum, A. cajennense, A. maculatum, Dermacentor andersoni, D. variabilis* and *Rhipicephalus sanguineus,* as well as the single-host ticks *D. albipictus* and *Boophilus microplus*, have been evaluated in the laboratory (Drummond et al., 1981; Nolan et al., 1981; Lancaster et al., 1982).

Under field conditions in South Africa (Schröder et al., 1985) and Zambia (Pegram and Lemche, 1985), multiple injections of ivermectin at intervals of 1 or 2 weeks reduced numbers of *B. decoloratus, H. truncatum, R. appendiculatus, A. hebraeum* and *A. variegatum* present on naturally infested cattle.

Ivermectin administered by means of sustained-release ear implants in cattle gave 70% control of *A. cajennense* and 85% control of *A. americanum* over a 7-week period (Miller et al., 1983).

A specially weighted osmotic pump for the administration of ivermectin to cattle at a controlled zero-order rate has been developed (Pope et al., 1985). Ivermectin administered by this system prevented the development of nematode infections (Egerton et al., 1986), and was highly effective in bringing about reproductive control of induced infestations of adult *A. hebraeum* on cattle (Soll et al., 1987).

This paper reports the results of two trials conducted to evaluate the efficacy of sustained-release ivermectin against 3 other economically important multihost tick species. Approximate dosage rates of 20, 40 and 60 $\mu g\ kg^{-1}\ day^{-1}$ were evaluated against induced infestations of *R. appendiculatus* in one trial, and dosages of approximately 40, 60 and 80 $\mu g\ kg^{-1}\ day^{-1}$ were evaluated against *R. evertsi* and *H. truncatum* in the other.

## MATERIALS AND METHODS

Twelve and 16 steers weighing approximately 200 kg were included in the two studies. Animals in each study were ranked by mass within breed and allocated to replicates of 4 animals each. Three replicates were included in the *R. appendiculatus* study, and animals within a replicate were randomly allocated to one of the following treatment groups: placebo-treated control; 1

ALZET[1] 2ML4 mini osmotic pump (designed to release ivermectin at 4 mg $day^{-1}$, or approximately 20 $\mu g\ kg^{-1}\ day^{-1}$ at a steady-state rate 7–28 days after administration); 2 ALZET 2ML4 pumps (approximately 40 $\mu g\ kg^{-1}\ day^{-1}$) or 3 ALZET 2ML4 pumps (approximately 60 $\mu g\ kg^{-1}\ day^{-1}$).

Four replicates were included in the *R. evertsi/H. truncatum* study. Animals within a replicate were randomly allocated either to an untreated control group or to treatment with 2, 3 or 4 ALZET 2ML4 osmotic pumps, resulting in treatment with ivermectin at dose rates of approximately 40, 60 or 80 $\mu g\ kg^{-1}\ day^{-1}$, respectively.

Cattle were housed either in specially designed cattle crates with anti-grooming stanchions or tethered in stalls to prevent grooming or interference with tick infestations.

In the trial against *R. appendiculatus*, an area around the base of each ear was shaved. In the *R. evertsi/H. truncatum* trial, four areas (two on each side of the midline) on the backs of the animals were shaved. Specially designed linen and leather bags were glued to these areas using contact adhesive. The 'free' end of the bag was fitted with a 'Velcro'®[2] strip which facilitated daily opening and closing of the bag for inspection. Bags were attached at least 1 day before infestation with ticks to allow fumes from the contact adhesive to dissipate. Before infestation, ticks were assessed for mobility to ensure that all were viable.

In the *R. appendiculatus* trial, 50 each of male and female unfed ticks were placed in the bag on the right ear on Day 7. The process was repeated for the left ear on Day 14.

For the *R. evertsi/H. truncatum* trial, 30 unfed adult *H. truncatum* (equal numbers of each sex) were placed in each of two bags and 28 unfed adult *R. evertsi* (equal numbers of each sex) were placed in each of the other two bags on each animal on Day 7 after treatment. A total of 120 *H. truncatum* and 112 *R. evertsi* ticks of each sex was thus placed for each of the four treatment groups.

The numbers of ticks that failed to attach or that fed and detached were recorded for each bag daily. Live unattached ticks were left in the bags and dead and engorged ticks were removed. Sixteen days after placement of *R. appendiculatus*, and 21 days after placement of *R. evertsi* and *H. truncatum*, all unattached ticks were removed, sexed, and assessed for viability and stage of engorgement. All fully engorged female ticks were removed daily, weighed, placed in individual weighed glass vials and incubated at approximately 28 °C and 80% relative humidity. Thereafter, the dates of onset of egg-laying, completion of egg-laying and onset of egg-hatching were recorded.

Spent female ticks were removed from the vial approximately 16 days (*H. truncatum*) or 21 days (*R. evertsi* and *R. appendiculatus*) after the onset of

[1]Trademark of ALZA Corp., Palo Alto, Cal., U.S.A.
[2]®Trademark of Velcro, New Hampshire, U.S.A.

egg-laying, and the vial and eggs weighed to enable calculation of the mass of eggs laid.

Egg size (no. eggs $mg^{-1}$) was estimated for up to 10 *Hyalomma* and *R. evertsi* ticks for each animal, if available, and for each *R. appendiculatus* that laid eggs, by weighing and counting an aliquot of eggs.

Each vial was examined approximately 4 weeks after completion of egg-laying and the percentage hatch of eggs visually estimated.

*Evaluation of data*

Where more male or female ticks were recovered than the number believed to have been placed (i.e. 16 *H. truncatum* or 15 *R. evertsi*) the number recovered was used as the number placed.

Two bags containing *H. truncatum* were removed by the animals late in the study and an unknown number of ticks was lost. The data from these bags were not used in any calculation.

The proportion of dead males, dead females and engorged females recovered was calculated for each bag on each animal and transformed, using the double-arcsine procedure (Freeman and Tukey, 1950). The mean retransformed proportion (Miller, 1978) was multiplied by the number placed to calculate the mean number of each type recovered.

The egg-mass:tick-mass ratio and proportion hatch were transformed using the angular transformation (Snedecor and Cochran, 1980). The egg-size values (eggs $mg^{-1}$) were averaged for each animal (*H. truncatum* and *R. evertsi*) and multiplied by the mass of eggs laid to estimate the total number of eggs laid by each tick. For *R. appendiculatus*, the individual tick data were used.

The index of reproduction (IR) was calculated for each tick by multiplying the number of eggs laid by proportion hatch. The number of eggs and IR were transformed to the natural logarithm of (value + 1).

Three time-intervals were calculated for each tick that engorged and was incubated: days to engorgement; days from engorgement to onset of egg-laying; and days from onset of egg-laying to onset of hatching. If a tick laid no eggs or if the eggs did not hatch, the interval value was assumed to be non-existent. Ticks that did not lay eggs were given a zero value for mass of eggs, number of eggs, and IR, and an unknown value for percent hatch. Ticks that did not produce larvae were assigned an IR of zero regardless of the reason (i.e., died, did not engorge, did not lay eggs, eggs did not hatch).

Four animals in the *R. evertsi/H. truncatum* trial were found to have drug remaining in the boluses when the cattle were slaughtered on Day 29. The data for these 4 animals were not included in the treatment means. The data were not statistically analysed because there were too few replicates remaining for meaningful analysis after excluding these animals.

## RESULTS

### *Efficacy against R. appendiculatus (Table 1)*

No ticks placed on cattle treated at 40 and 60 $\mu g\ kg^{-1}\ day^{-1}$ were able to reproduce successfully. Only a few females placed on animals treated at 20 $\mu g\ kg^{-1}\ day^{-1}$ engorged. For these ticks, the time required for engorgement and the time from engorgement to onset of egg-laying were longer than for control ticks. Ticks engorging on ivermectin-treated animals had a lower mass when engorged and laid smaller egg-masses, both absolutely and as a proportion of

TABLE 1

Efficacy of ivermectin against induced infestations of *Rhipicephalus appendiculatus*

| Variable | Ivermectin level ($\mu g\ kg^{-1}\ day^{-1}$) | | | |
|---|---|---|---|---|
| | Control | 20 | 40 | 60 |
| Number of animals | 3 | 3 | 3 | 3 |
| Bags/animal | 2 | 2 | 2 | 2 |
| Ticks/bag | | | | |
| Females | 50 | 50 | 50 | 50 |
| Males | 50 | 50 | 50 | 50 |
| Dead ticks recovered[1] | | | | |
| Females | 10.6 | 28.0 | 18.7 | 21.8 |
| Males | 2.6 | 5.9 | 11.5 | 16.5 |
| Engorged females recovered[1] | 31.6 | 0.2 | 0 | 0 |
| Days to engorgement[2] | 8.1 | 12.5 | – | |
| | | | – | |
| Days from engorgement to onset of egg-laying[2] | 5.1 | 15.0 | – | – |
| Days from onset to end of egg-laying[2] | 17.0 | 17.0 | – | – |
| Days from onset of egg-laying to onset of hatch[2] | 23.5 | 17.0 | – | – |
| Weight of engorged females[2] (mg) | 497 | 114 | – | – |
| Weight of egg mass[2] (mg) | 276 | 12 | – | – |
| Egg weight: tick weight[3] (%) | 52.0 | 6.9 | – | – |
| Egg size[2] (eggs $mg^{-1}$) | 26.2 | 45.5 | – | – |
| Eggs laid[4] (no.) | 3800 | 31 | – | – |
| Hatched eggs[3] (%) | 91.2 | 65.8 | – | – |
| Index of reproduction[5] | 133.6 | 0.04 | 0 | 0 |
| Percentage control | – | >99.9 | 100 | 100 |

[1]Retransformed mean of radians, multiplied by number placed; the proportion was transformed using the double-arcsine procedure.
[2]Arithmetic mean.
[3]Retransformed mean of radians; the proportion was transformed using the arcsine/square-root procedure.
[4]Geometric mean; the number of eggs was transformed to ln (number + 1).
[5]Geometric mean; the sum of ln (index + 1) for each female tick in a bag was divided by the number initially placed.

engorged mass. The eggs tended to be smaller and not to hatch as well as those from untreated animals. The index of reproduction was reduced by more than 99.9% at 20 $\mu g\ kg^{-1}\ day^{-1}$ and 100% at 40 and 60 $\mu g\ kg^{-1}\ day^{-1}$.

*Efficacy against R. evertsi (Table 2)*

Mortality of male and female ticks was higher for ticks placed on ivermectin-treated animals than for those placed on controls. The number of female ticks engorging decreased as the daily dosage of ivermectin increased, and they took more than twice as long to engorge as those placed on untreated animals. Ticks

TABLE 2

Efficacy of ivermectin against induced infestations of *Rhipicephalus evertsi*

| Variable | Ivermectin level ($\mu g\ kg^{-1}\ day^{-1}$) | | | |
|---|---|---|---|---|
| | Control | 40 | 60 | 80 |
| Number of animals | 4 | 4 | 2 | 2 |
| Bags/animal | 2 | 2 | 2 | 2 |
| Ticks/bag[1] | | | | |
| Males | 14.1 | 14.0 | 14.2 | 14.2 |
| Females | 14.1 | 14.0 | 14.0 | 4.0 |
| Dead ticks recovered[2] | | | | |
| Males | 0.6 | 4.1 | 2.6 | 4.9 |
| Females | 1.2 | 6.9 | 7.0 | 5.4 |
| Engorged females recovered[2] | 12.6 | 2.4 | 0.2 | 0.5 |
| Females laying eggs[2] | 12.2 | 1.2 | 0.1 | 0.3 |
| Days to engorgement[3] | 8.3 | 18.9 | 19.0 | 18.0 |
| Days from engorgement to onset of egg laying[3] | 4.7 | 5.1 | 7.0 | 4.0 |
| Days from onset of egg-laying to onset of hatch[3] | 23.6 | 32.0 | – | – |
| Weight of engorged females[3] (mg) | 846 | 352 | 390 | 140 |
| Weight of egg mass[3] (mg) | 451 | 15 | 15 | 13 |
| Egg weight: tick weight[4] (%) | 51.7 | 1.8 | 2.3 | 6.6 |
| Egg size[3] (eggs $mg^{-1}$) | 32.5 | 62.9 | 29.0 | 58.5 |
| Eggs laid[5] | 9488 | 14.4 | 1.3 | 12.0 |
| Hatched eggs[4] (%) | 99.6 | 0.2 | 0 | 0 |
| Index of reproduction[6] | 2848 | 0.06 | 0 | 0 |
| Percentage control | – | >99.9% | 100% | 100% |

[1]Harmonic mean.
[2]Retransformed mean of radians, multiplied by number placed; the proportion was transformed using the double-arcsine procedure.
[3]Arithmetic mean.
[4]Retransformed mean of radians; the proportion was transformed using the arcsine/square-root procedure.
[5]Geometric mean; the number of eggs was transformed to ln (number + 1).
[6]Geometric mean: the sum of ln (index + 1) for each female tick in a bag was divided by the number initially placed.

engorging on ivermectin-treated cattle had a lower mass when engorged and laid smaller egg-masses, both absolutely and as a proportion of engorged mass. The eggs tended to be smaller and have a lower rate of hatch. No tick fed on cattle treated at 60 and 80 $\mu$g kg$^{-1}$ day$^{-1}$ was able to reproduce successfully; although a few ticks engorged and laid eggs, none of these eggs hatched. The index of reproduction was reduced by more than 99.9% at 40 $\mu$g kg$^{-1}$ day$^{-1}$ and 100% at 60 and 80 $\mu$g kg$^{-1}$ day$^{-1}$.

TABLE 3

Efficacy of ivermectin against induced infestations of *Hyalomma truncatum*

| Variable | Ivermectin level ($\mu$g kg$^{-1}$ day$^{-1}$) | | | |
|---|---|---|---|---|
| | Control | 40 | 60 | 80 |
| Number of animals | 4 | 4 | 2 | 2 |
| Bags/animal | 2[1] | 2 | 2 | 2[1] |
| Ticks/bag[2] | | | | |
| Males | 15.0 | 14.9 | 15.0 | 15.0 |
| Females | 15.1 | 15.0 | 15.0 | 15.0 |
| Dead ticks recovered[3] | | | | |
| Males | 1.2 | 4.6 | 8.0 | 10.8 |
| Females | 0.4 | 6.4 | 0.3 | 12.6 |
| Engorged females recovered[3] | 14.3 | 0 | 0 | 0 |
| Females laying eggs[3] | 11.2 | 0 | 0 | 0 |
| Days to engorgement[4] | 9.0 | - | - | - |
| Days from engorgement to onset of egg-laying[4] | 5.9 | - | - | - |
| Days from onset of egg-laying to onset of hatch[4] | 21.8 | - | - | - |
| Weight of engorged females[4] (mg) | 531 | - | - | - |
| Weight of egg mass[4] (mg) | 239 | - | - | - |
| Egg weight: tick weight[5] (%) | 38.7 | - | - | - |
| Egg size[4] (eggs mg$^{-1}$) | 39.1 | - | - | - |
| Eggs laid[6] | 1512 | - | - | - |
| Hatched eggs[5] (%) | 89.8 | - | - | - |
| Index of reproduction[7] | 416 | 0 | 0 | 0 |
| Percentage control | - | 100 | 100 | 100 |

[1]An unknown number of ticks were lost from one bag on one animal.
[2]Harmonic mean.
[3]Retransformed mean of radians, multiplied by number placed; the proportion was transformed using the double-arcsine procedure.
[4]Arithmetic mean.
[5]Retransformed mean of radians; the proportion was transformed using the arcsine/square-root procedure.
[6]Geometric mean; the number of eggs was transformed to ln (number + 1).
[7]Geometric mean; the sum of ln (index + 1) for each female tick in a bag was divided by the number initially placed.

*Efficacy against H. truncatum (Table 3)*

Mortality of both male and female ticks compared to controls increased as the daily dose of ivermectin increased. No tick placed on ivermectin-treated animals engorged; thus, the index of reproduction was reduced 100% at 40, 60 and 80 $\mu g\ kg^{-1}\ day^{-1}$.

## DISCUSSION

Although ivermectin at daily dosages of approximately 40 $\mu g\ kg^{-1}\ day^{-1}$ and greater caused increased mortality of both male and female ticks, the most important measure of control is the reproductive potential of the female tick.

For *H. truncatum* and *R. appendiculatus*, no females engorged on animals treated at dosages of 40 $\mu g\ kg^{-1}\ day^{-1}$ and higher. The reproductive index of these ticks was 0, which resulted in 100% reproductive control. Small numbers (1.4–3.6%) of female *R. evertsi* engorged on animals treated at 60 and 80 $\mu g\ kg^{-1}\ day^{-1}$. These ticks were small and laid very few eggs, which did not hatch. The reproductive index of these ticks was also 0, and reproductive control of *R. evertsi* was therefore also 100% at dosages of 60 and 80 $\mu g\ kg^{-1}\ day^{-1}$. A small number of female *R. appendiculatus* (0.4%) placed on animals treated at 20 $\mu g\ kg^{-1}\ day^{-1}$, and 17.1% of *R. evertsi* placed on animals treated at 40 $\mu g\ kg^{-1}\ day^{-1}$ did partially engorge. These ticks were smaller and laid egg-masses of approximately 50% of the weight of those laid by the control ticks. The eggs also had a low percentage hatch. As a result, the index of reproduction of these ticks was also reduced by more than 99.9% relative to that of untreated controls.

These data support the findings of Drummond et al. (1981), who reported that female ticks engorging on ivermectin-treated animals take longer to engorge, usually weigh less, and lay smaller egg-masses than females engorging on untreated animals. In the present studies, ticks placed on treated animals usually attached normally, but only partially engorged. They remained attached and partially engorged for long periods. Sometimes they detached and wandered around in the bags before dying.

*Rhipicephalus appendiculatus* appears to be particularly sensitive to low levels of ivermectin. Mortalities were relatively high, and very low numbers of engorged females (0.4%) were recovered from cattle treated at 20 $\mu g\ kg^{-1}\ day^{-1}$.

*Hyalomma truncatum* also appears to be very sensitive to sustained-release ivermectin. No female tick engorged on any animal treated at levels of 40 $\mu g\ kg^{-1}\ day^{-1}$ and higher, although the mortality rate was lower than for *R. appendiculatus*.

In these studies, *R. evertsi* was the least-sensitive parasite. Small numbers of female ticks engorged on animals treated at all dose rates, although none of those from animals treated at 60 and 80 $\mu g\ kg^{-1}\ day^{-1}$ laid eggs and the reproductive index was reduced by more than 99.9% for treatment at dosages of 40 $\mu g\ kg^{-1}\ day^{-1}$ and higher.

The success of ivermectin treatment depends upon the attachment and at least partial engorgement of ticks. The causative organisms of various tick-borne diseases (eg. theileriosis) and the toxins responsible for toxicoses (e.g. sweating-sickness) are transmitted as ticks feed. It has been reported that ivermectin is detrimental to tick salivary-gland function (Kaufmann et al., 1986). The influence that ivermectin-induced impairment of salivary function and reduced tick engorgement may have on disease transmission and tick toxicoses remains to be determined.

M.D. Soll (unpublished observations, 1987) found that many *A. hebraeum* and *R. evertsi* nymphae which engorged on animals treated with ivermectin at approximately 40 $\mu g\ kg^{-1}\ day^{-1}$ did not moult successfully. Centurier and Barth (1980) have also reported a reduction in moulting rates of nymphae of *Ornithodoros moubata* and *R. appendiculatus* fed on cattle treated with ivermectin subcutaneously at 100 $\mu g\ kg^{-1}$ and higher. It is possible that this detrimental effect on the development of immature stages may further influence the transmission of tick-borne diseases by multihost ticks.

Sustained blood-levels of ivermectin can be provided in cattle for a period of months (Pope et al., 1985). Administration of a sustained-release device shortly before the seasonal peak of adult tick activity could substantially reduce contamination of pastures with progeny from feeding ticks. Benefits of sustained ivermectin treatment may only be seen later in the season, or the following year consequent to the reductions in reproductive potential of the treated generation. This concept needs to be tested in the field with a system designed to provide ivermectin release over an extended period.

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