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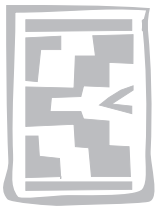

Protective efficacy of isometamidium chloride and diminazene aceturate against natural *Trypanosoma brucei*, *Trypanosoma congolense* and *Trypanosoma vivax* infections in cattle under a suppressed tsetse population in Uganda

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ABSTRACT

MAGONA, J.W., MAYENDE, J.S.P., OKIRIA, R. & OKUNA, N.M. 2004. Protective efficacy of isometamidium chloride and diminazene aceturate against natural *Trypanosoma brucei, Trypanosoma congolense* and *Trypanosoma vivax* infections in cattle under a suppressed tsetse population in Uganda. *Onderstepoort Journal of Veterinary Research*, 71:231–237

The protective efficacy of isometamidium chloride (ISMM) and diminazene aceturate (DIM) against *Trypanosoma brucei*, *Trypanosoma congolense* and *Trypanosoma vivax* infections in cattle under a suppressed tsetse population was assessed in southeast Uganda. A total of 66 and 57 trypanosome-infected cattle were treated with ISMM and DIM, respectively together with 177 trypanosome-free animals not treated were followed for 12 months, checked every 4 weeks. There was no statistical difference in the mean time to infection with any trypanosome species in animals treated with ISMM or DIM. However, the mean time to trypanosome infection was significantly longer for treated animals than controls. The mean time to infection with each of the three trypanosome species differed significantly, with the average time to *T. vivax* infection the lowest, followed by *T. congolense* and then *T. brucei*. The protective efficacy of DIM was as good as that of ISMM; implying curative treatments against trypanosomosis are sufficient for combination with tsetse control. Isometamidium chloride or DIM had the highest impact on *T. brucei* and *T. congolense* infections in cattle.

Keywords: Diminazene aceturate, isometamidium chloride, protective efficacy, suppressed tsetse population

INTRODUCTION

Tsetse flies (*Glossina* spp.) are estimated to infest 106 400 km^2, 50 % of the entire surface area of Uganda and 2.2 million head of cattle of the estimated national cattle population of 5.4 million are at risk of trypanosomosis (Chizyuka 1998). It is estimated that tsetse infestation and incidence of trypanosomosis has prevented the keeping of an extra 3.3 million head of cattle in Uganda (Chizyuka 1998). Existing reports indicate the prevalence of trypanosomosis in cattle in Uganda to be 11.9 % under the intensive dairy system and 25 % under the communal grazing systems (Magona & Mayende 2002).

In the past, control of tsetse and both human and animal trypanosomosis in southeast Uganda was achieved successfully through a donor-funded large-scale deployment of insecticide-impregnated traps (Lancien, Muguwa, Lannes & Bouvier 1990) integrated with limited application of pour-on and chemotherapy against animal trypanosomosis (Magona, Okuna, Katabazi, Okoth, Omollo, Mayende &

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Drabile 1998). Direct application of deltamethrin pour-on on cattle has been used to successfully control *Glossina fuscipes fuscipes* in southeast Uganda (Magona *et al.* 1998; Okiria, Okuna, Magona & Mayende 2002).

Control of animal trypanosomosis in Uganda has relied on the use of both diminazene aceturate (DIM) and isometamidium chloride (ISMM) for the last 30 years (Mwambu & Mayende 1971; Rushigajiki, Mayende, Guloba & Wilson 1986; Okuna, Magona, Okiria & Mayende 1993a; Okuna, Magona & Mayende 1993b). These trypanocidal drugs in many African countries such as Uganda are reported to be popular with livestock owners and veterinarians probably because they are affordable and effective (Geerts & Holmes 1999). Repeated use of trypanocidal drugs has led to emergence of drug resistance. Strains of trypanosomes resistant to diminazene aceturate have been reported in Uganda (Mwambu & Mayende 1971; Matovu, Iten, Enyaru, Schmid, Lubega, Brun & Kaminsky 1997). However, latest reports by Olila, McDermott, Eisler, Mitema, Patzelt, Clausen, Poetzsch, Zessin, Mehlitz & Peregrine (2002), revealed diminazene aceturate and isometamidium chloride were still effective against trypanosome isolates obtained from some sites in southeast Uganda, where farmers routinely used trypanocidal treatments against animal trypanosomosis.

Despite this optimistic report, it is imperative to guard against the emergence of trypanocidal resistance. Integration of tsetse control and trypanocidal drug use has been determined to be an effective method to counteract either single or multiple drug resistance (Fox, Mmbando, Fox & Wilson 1993; Leak, Peregrine, Mulatu, Rowlands, D'Ieteren 1996) and is recommended for the prevention of emergence of trypanocidal drug resistance (Geerts & Holmes 1999).

In either large-scale or farmer-level animal trypanosomosis campaigns involving integration of vector control with trypanocidal drug use, project managers or farmers often face difficulties in deciding whether to select a curative drug—diminazene aceturate—or a prophylactic one—isometamidium chloride—to combine with vector control. Field reports on the protective efficacy of either diminazene aceturate or isometamidium chloride under suppressed tsetse populations are rare. In this paper a study conducted in southeast Uganda to evaluate the protective efficacy of diminazene aceturate and isometamidium chloride combined with application of deltamethrin pour-on is described.

MATERIALS AND METHODS

Study area

The study was conducted at Masaba in Busia district, southeast Uganda. Location, farming system, climate and vegetation of the study area have been described previously (Okiria *et al.* 2002). *Glossina f. fuscipes* is the main tsetse species in the area, but *Glossina pallidipes* also exists in low densities (Magona, Katabazi, Olaho-Mukani, Mayende & Walubengo 1997; Okiria *et al.* 2002). The main tsetse control method in the study area was deltamethrin pour-on applied on cattle (Okiria *et al.* 2002). This tsetse control programme maintained the tsetse density in the study area between 0 and 0.5 flies per trap per day (Okiria *et al.* 2002)—a situation herein described as a suppressed tsetse population.

Cattle

Three hundred Zebu cattle of all ages and both sexes kept under a communal grazing system were used in the study. Sixty-six of the cattle composed of 26 naturally infected with *Trypanosoma brucei*, 14 infected with *Trypanosoma congolense* and 26 infected with *Trypanosoma vivax* were ear-tagged and treated with ISMM by intramuscular injection at a dosage rate of 0.5 mg/kg body mass. Another group of 57 cattle consisted of 24 infected with *T. brucei,* 15 infected with *T. congolense* and 18 infected with *T. vivax* were ear-tagged and treated with DIM by intramuscular injection at a dosage rate of 7.0 mg/kg body mass. A group of 177 trypanosome-free cattle belonging to the same herds and kept under the same challenge of trypanosomosis than the treated cattle were left untreated but included in the study as controls. There was a similar composition of animals according age groups and sex between the treated and control groups.

All the 300 cattle were examined every 4 weeks for a period of 12 months for trypanosome infections, using the Buffy coat technique (Murray, Murray & McIntyre 1977). Trypanosomes were specifically identified under a standard microscope. Cattle that became re-infected were treated with DIM at a dosage rate of 7.0 mg/kg body mass.

Data analysis

For purposes of data analysis, an animal was excluded as soon as it became re-infected to avoid being counted again with an infection of a different trypanosome species. Survival analysis was used

to compare the protective efficacy of ISMM and DIM to infection with different trypanosome species. All analyses were performed in GLIM, version 6, using the method outlined by Crawley (1993). Since not all animals became infected during the course of the study, a censoring indicator was assigned to each individual: animals that became infected were scored as 1, and those that remained trypanosome-free on the last parasitological examination were scored 0. Survival time was defined as either the month parasites were first detected (for infected animals) or the month of last parasitological examination (for non-infected animals). The censoring indicator (1/0 score) was set as the response variable and assigned Poisson errors. A log-linear hazard model was fitted to the data with natural log of survival time declared as an offset.

Treatment regimen was fitted to the model as a factorial explanatory variable with three levels, namely 1 for controls, 2 for ISMM-treated animals, and 3 for those treated with DIM. Significant difference between the ISMM and DIM groups was tested by combing levels 2 and 3 of the treatment regimen variable, and comparing the increase in deviance to the value in the chi-square table with one degree of freedom. If the grouping of ISMM and DIM animals into a single treated group was achieved without a significant loss of explanatory power, the model simplification was accepted. Difference between treated animals (ISMM and DIM-treated animals combined) and controls was tested by combining levels: grouping treated and control animals together and comparing the change in deviance to the chi-square table with one degree of freedom. The survival analysis was carried out for each trypanosome species (*T. brucei*, *T. congolense* and *T. vivax*) separately.

A similar procedure was used to test differences between the survival times to infection with different species of trypanosome in control animals. The explanatory variable was trypanosome species with three levels, 1 for *T. brucei*, 2 for *T. congolense* and 3 for *T. vivax*). The log-linear hazard model assumed a constant hazard function, which is equivalent to the force of infection, which is the instantaneous rate at which animals acquire trypanosome infections. The reciprocal of the hazard function is the mean time to infection, which is reported, together with 95 % confidence intervals, for the significant groupings from the different survival analyses.

RESULTS

Infections with mixed trypanosome species were rarely detected in the experimental cattle. Of the 177 control animals, 55 were infected with at least one trypanosome species, 16 with *T. brucei* only, 13 with *T. congolense* only, and 26 with *T. vivax* only during the first infections. Over the entire 12 months 21 *T. brucei* (21/177), 36 *T. congolense* (36/177) and 133 *T. vivax* infections (133/177) were detected among the control cattle. Among the 66 treated with ISMM, there were no re-infections in animals that originally had *T. brucei* infections (0/26), five re-infections for those that had *T. congolense* (5/14) and eight re-infections in those that had *T. vivax* infections (8/26) over a period of 12 months. Among the 57 treated with DIM, there were two re-infections in those that had *T. brucei* infections (2/24), one re-infection in those that had *T. congolense* infections (1/15) and four re-infections in those that had *T. vivax* infections (4/18).

The mean time to infection with each of the three trypanosome species is shown in Table 1. The mean time to infections of the various trypanosome species differed significantly ($\chi^2 = 166.30$, d.f. = 2, $P < 0.01$), with the average time to *T. vivax* infection being lowest, followed by *T. congolense* and then *T. brucei* infection.

There was no statistical difference in the mean time to infection with any trypanosome in animals treated with ISMM or DIM ($\chi^2 = 0.943$, d.f. = 1, $P > 0.05$), and the mean time to infection was significantly

TABLE 1 The mean time, in months, to infection (with 95 % confidence intervals) for control and treated cattle (ISMM and DIM groups combined) in under a suppressed tsetse population in southeast Uganda estimated from the survival analyses

Trypanosome species	Mean months to infection (95 % confidence intervals)	
	Controls	Treated
T. brucei	83.9 (54.7–128.7)	667.1 (170.2–2614.8)
T. congolense	48.5 (35.0–67.2)	224.5 (101.7–495.9)
T. vivax	9.2 (7.7–10.9)	83.9 (60.6–187.7)
Any trypanosome species	5.1 (4.5–5.9)	62.9 (40.8–96.9)

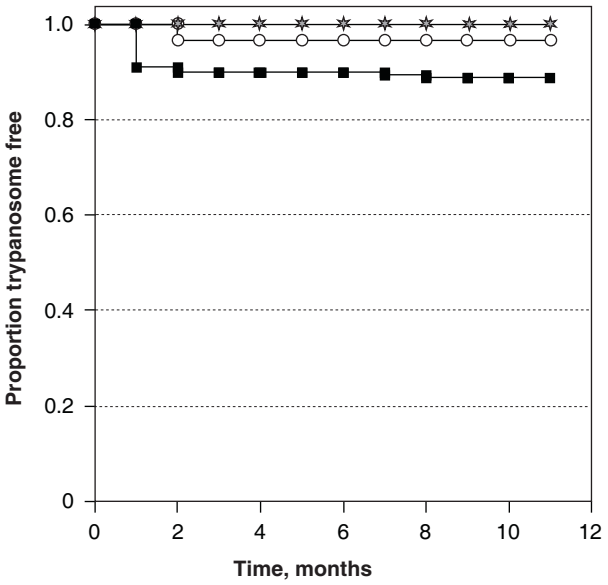

FIG. 1 Proportion of control (filled squares), ISMM-treated (stars) and DIM-treated (open circles) cattle free of *T. brucei* infections under a suppressed tsetse population in southeast Uganda

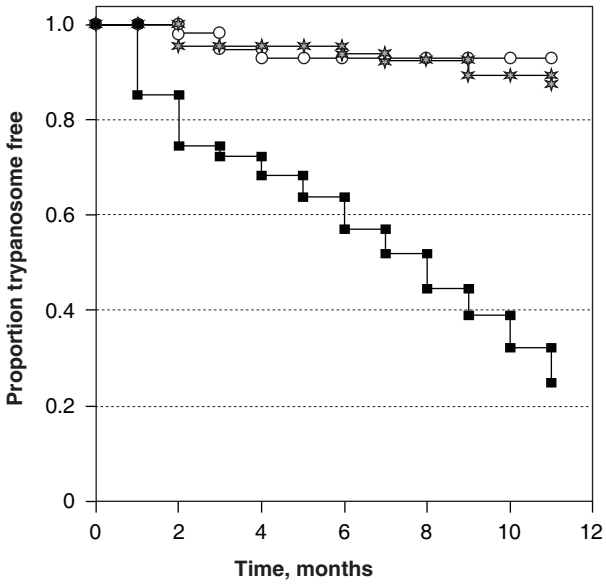

FIG. 3 Proportion of control (filled squares), ISMM-treated (stars) and DIM-treated (open circles) cattle free of *T. vivax* infections under a suppressed tsetse population in southeast Uganda

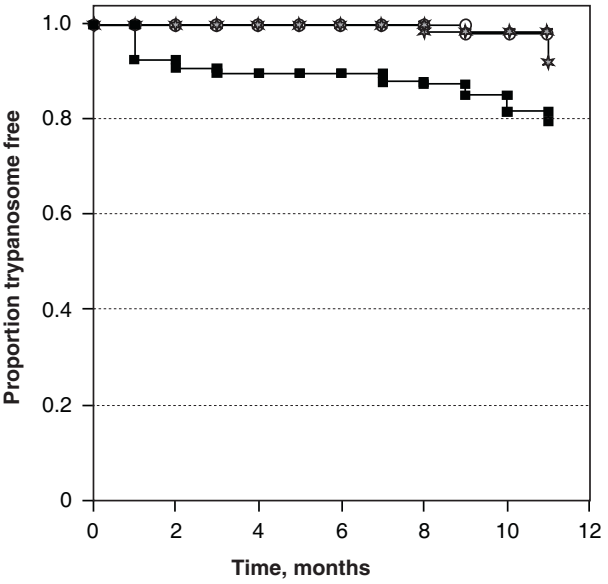

FIG. 2 Proportion of control (filled squares), ISMM-treated (stars) and DIM-treated (open circles) cattle free of *T. congolense* infections under a suppressed tsetse population in southeast Uganda

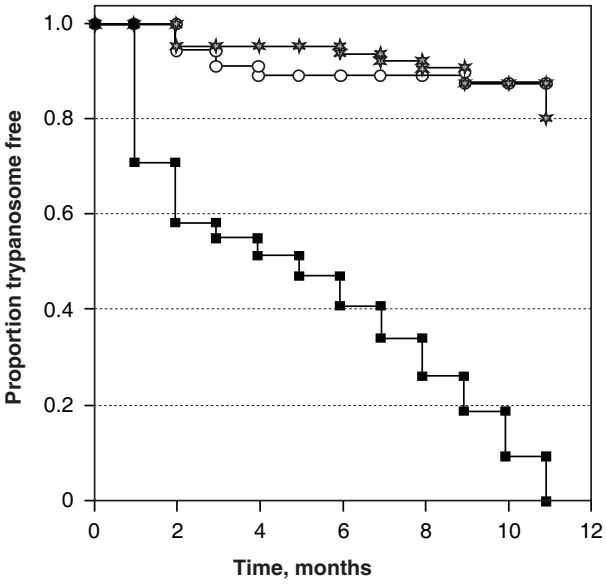

FIG. 4 Proportion of control (filled squares), ISMM-treated (stars) and DIM-treated (open circles) cattle free of infections with any trypanosome species under a suppressed tsetse population in southeast Uganda

longer for treated animals than controls ($\chi^2 = 205.6$, d.f. = 1, $P < 0.01$).

No statistical difference in the mean time to infection with *T. brucei* in animals treated with ISMM or DIM ($\chi^2 = 3.13$, d.f. = 1, $P > 0.05$) was noted and the mean time to infection was also significantly longer for treated animals than controls ($\chi^2 = 13.46$, d.f. = 1, $P < 0.01$).

There was also no statistical difference in the mean time to infection with *T. congolense* in animals treated with ISMM or DIM ($\chi^2 = 2.36$, d.f. = 1, $P > 0.05$), and the mean time to infection was signifi-

cantly longer for treated animals than controls (χ^2 = 16.73, d.f. = 1, $P < 0.01$).

There was no statistical difference in the mean time to infection with *T. vivax* in animals treated with ISMM or DIM (χ^2 = 0.851, d.f. = 1, $P > 0.05$). The mean time to infection was significantly longer for treated animals than controls (χ^2 = 124.2, d.f. = 1, $P > 0.01$).

The proportion of *T. brucei*-infected cattle that remained free of re-infection after either ISMM or DIM treatment and the untreated cattle that remained free of *T. brucei* infection is shown in Fig. 1. The ISMM-treated group had the highest proportion of cattle free of *T. brucei* re-infection, followed by the DIM-treated group and then the untreated group.

The proportion of *T. congolense*-infected cattle that remained free of re-infection after either ISMM or DIM treatment and the untreated cattle that remained free of *T. congolense* infection is shown in Fig. 2. Both the ISMM-treated and DIM-treated groups had a high and similar proportion of cattle free of *T. congolense* re-infection, which was higher than that of the untreated group. But the untreated group had a reasonably high proportion of cattle free of *T. congolense* infection.

The proportion of *T. vivax*-infected cattle that remained free of re-infection after either ISMM or DIM treatment and the untreated cattle that remained free of *T. vivax* infection is shown in Fig. 3. Although both ISMM-treated and DIM-treated groups had a high and similar proportion of cattle that were free of *T. vivax* re-infection, the untreated group had a very low proportion of cattle (20 %) that remained free of *T. vivax* infection.

In Fig. 4 the proportion of trypanosome-infected cattle in general that remained free of re-infection after either ISMM or DIM treatment, and the untreated group that remained free of infection with any trypanosome species is shown. Both ISMM and DIM-treated groups had a high and similar proportion of cattle that remained free of re-infection with any trypanosome species, but after approximately 11 months, all untreated cattle had been infected at least once with any trypanosome species.

DISCUSSION

The selection of infected animals for the ISMM-treated and DIM-treated groups might have introduced an interfering factor such as possible development of immunity by animals because of recent trypanosomal infections, however, infected animals were used for purposing of assessing the efficacy of the two trypanocidal drugs, ISMM and DIM under field conditions. Infections with mixed trypanosome species were rarely detected probably because of differences in the sensitivity of the different trypanosome species to trypanocidal drugs and being affected differently by vector control. The mean time to infections of the various trypanosome species differed significantly, with the average time to *T. vivax* infection being lowest, followed by *T. congolense* and then *T. brucei* infection. This finding on the mean time to infection of the various trypanosome species reflects the developmental periods for the various trypanosome species in the tsetse vector, being shortest for *T. vivax* hence allowing its infection rate to build up faster during control programmes than those for *T. congolense* and *T. brucei* (Magona, Greiner & Mehlitz 2000; Okiria *et al*. 2002). Other field studies conducted in southeast Uganda have reported a drastic decline of *T. brucei* infection in cattle following treatment with DIM at a dosage rate of 7 mg/kg body mass (Rushigajik *et al.* 1986).

There was no statistical difference in the mean time to infection with *T. brucei, T. congolense* or *T. vivax* in animals treated with ISMM or DIM, but for all three the trypanosome species the mean time to infection was significantly longer for treated animals than controls. The general practice in the use of both ISMM and DIM in the control of animal trypanosomosis, involves treatment of animals with ISMM every 3 months because the prophylactic period is expected to last for this period, while DIM is used as a curative drug against trypanosomosis whenever there are cases. Diminazene aceturate is used to clear trypanosome reservoir infection in animals but it is expected to protect animals for only 2 weeks. It is evident from this study that combination of diminazene's excellent property of clearing reservoir infection in animals when the dosage of 7.0 mg/kg body mass is used with vector control attains a protective efficacy against any trypanosome species, which is as long as that achieved when the isometamidium chloride is used at the dosage of 0.5 mg/kg body mass and combined with vector control. This phenomenon could probably be attributed to the interplay of the reduced tsetse challenge and disease transmission due to vector control, and possible developed of immunity in cattle that have had recent trypanosomal infection but treated as well the effect of drug prophylaxis. These findings imply, as regards protective efficacy, either diminazene aceturate or isometamidium chloride can be select-

ed for combination with vector control. Under such a trypanosomosis control strategy, selection of the trypanocide has to be based on the cost of the drug and the targeted animal health improvement rather than the protective efficacy.

The ISMM-treated group had the highest proportion of cattle free of *T. brucei* re-infection, followed by the DIM-treated group and then the untreated group, which implies that *T. brucei* infection was more sensitive to ISMM than to DIM. Other workers have also reported that *T. brucei* isolates from southeast Uganda are sensitive to DIM and ISMM (Olila *et al.* 2002).

Both the ISMM-treated and DIM-treated groups had a high and similar proportion of cattle free of *T. congolense* re-infection, which was higher than that of the untreated group. But the untreated group had a reasonably high proportion of cattle free of *T. congolense* infection. It is evident that *T. congolense* infections were equally sensitive to both of the trypanocidal drugs ISMM and DIM.

Although both ISMM-treated and DIM-treated groups had a high and similar proportion of cattle that were free of re-infection with trypanosomes, the untreated group had a very low proportion of cattle (20 %) that remained free of *T. vivax* infection. *Trypanosoma vivax* isolates from southeast Uganda have been reported to be sensitive to ISMM and DIM (Olila *et al.* 2002), but, during control programmes involving either chemotherapy or vector control in southeast Uganda, *T. vivax* infections in cattle have been observed to predominate over other trypanosome species (Magona *et al.* 1998; Magona *et al.* 2000; Okiria *et al.* 2002) due to its shorter developmental period (4–5 days) in the tsetse vector than that of other trypanosome species *T. brucei* or *T. congolense.*

Both the ISMM-treated and DIM-treated groups had a high and similar proportion of cattle that remained free of re-infection with any trypanosome species, but after approximately 11 months, all untreated cattle had been infected at least once with any trypanosome species. This implies that despite the suppressed tsetse population, substantial transmission of trypanosomosis especially due to *T. vivax* was possible. Nevertheless, both ISMM and DIM maintained a satisfactory protective efficacy. These findings and the fact that there are only a small number of technical or anecdotal reports of the emergence of drug-resistant trypanosome populations in cattle in Uganda suggest that both ISMM and DIM are still effective against animal trypanosomosis. Even the few existing reports have either reported ineffectiveness of trypanocidal drugs for animal use on human infective trypanosomes (Matovu *et al.* 1997; Enyaru, Matovu, Lubega & Kaminsky 1998) or in one genuine incidence involving DIM, resistance was attributed to cross-resistance to DIM by probable quinapyramine-resistant trypanosome strains (Mwambu & Mayende 1971). This limited occurrence of drug resistance to both ISMM and DIM in Uganda could probably be because of the long tradition of integrating both trypanocidal drugs use with vector control (Lancien *et al.* 1990; Ndyabahinduka 1993; Magona *et al.* 1998) that has been advocated for over many years. Other studies on farmer control programmes against animal trypanosomosis in Mbarara district of Uganda, involving the application of deltamethrin pour-on combined with the routine use of ISMM have also revealed good efficacy of trypanocidal drugs (Okuna, unpublished data 2003).

In conclusion, a combination of trypanocidal drug use and vector control in the control of animal trypanosomosis, as demonstrated by these findings and others published elsewhere (Fox *et al.* 1993; Leak *et al.* 1996), has substantial potential in minimizing the occurrence of drug-resistant trypanosome strains. It is evident from this study that in such a control strategy either DIM (curative) or ISMM (prophylactic) could be used. The highest impact of this control strategy seems to be on *T. brucei* and *T. congolense* infections in cattle in southeast Uganda. These results confirm the effectiveness of the trypanocidal drugs ISMM and DIM against trypanosome infections despite the many years of their use in the fight against animal trypanosomosis in southeast Uganda.

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