

Endectocide treatment of the reindeer

Antti Oksanen



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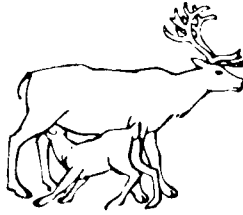
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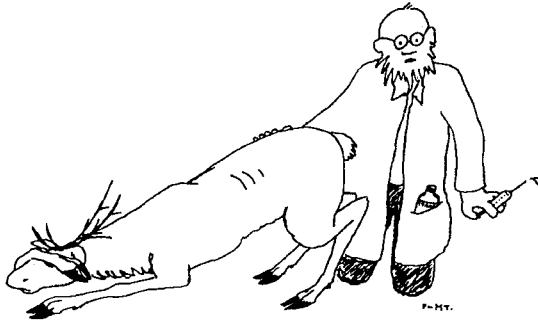
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Content

Content	5
Foreword	7
Abstract	9
Yhteenveto.....	10
Čeahkkáigeassu.....	11
Sammendrag	12
List of original publications.....	13
Abbreviations	14
Introduction	15
Parasite fauna of the reindeer and antiparasitic measures.....	16
Macrocyclic lactone endectocides	21
Aims of the research	29
Materials and methods.....	29
Results	31
Discussion.....	33
Conclusions	37
Acknowledgements.....	37
References	39
Appendixes	50



Foreword

Finnish veterinarians have traditionally been interested in research on the reindeer; 6 reindeer dissertations were presented at the College of Veterinary Medicine in Helsinki during its 5 decades (now Faculty at the University of Helsinki). There may be several reasons for it. The semi-domesticated reindeer forms a unique and exciting link between agriculture and wildlife. Reindeer husbandry is an important source of livelihood in northern Finland, where the nature does not favour other forms of agriculture. In addition, it is relatively easy to increase the knowledge of the reindeer, which is not a well-known animal species in the world veterinary community.

The work on this thesis started in 1989 with a comparison of two methods of administration of ivermectin. Then, as now, veterinary parasitologists reported excellent efficacy of ivermectin from clinical trials in different animal species in all parts of the world, and that was exactly what I expected to find. Although the starting point was not very exciting, I soon learned to like the practical aspects of the research as we found out that it was not all the same how ivermectin was administered to reindeer. This work was carried out at the Kaamanen Experimental Reindeer Herd. This herd is perhaps the one most suitable for controlled herd trials anywhere. I highly appreciate the possibility to work in this unique herd.

This work has not been done according to a prearranged plan, one discovery opened a new question and thus led to the next step. The work is practical by nature, and for some people working in another field, the methods may seem outdated. However, faecal egg counting can still be considered the most useful diagnostic method in veterinary parasitology.



Illustrations on pages 4, 6, and 8 by Päivi Teljosuo

Abstract

The semi-domesticated reindeer population of the world is almost 4 million animals, and the reindeer is essential for Arctic peoples, such as the Saami. In northern Finland, where unemployment is a big problem, about 1800 families get a major part of their living from reindeer husbandry, and the reindeer population (winter herd) amounts to about 200,000 animals. Antiparasitic treatment with pharmaceuticals, first a few years with organophosphates and, since the early 1980's with ivermectin (a macrocyclic lactone endectocide), has become a routine also in reindeer husbandry, with about 80 % of animals treated yearly in Finland.

The aim of the treatment is to strengthen the animals to survive winter, as well as to produce healthy offspring, and thus increase the income of the reindeer owner. Ivermectin treatment has mainly been given by subcutaneous (sc) injection, but ease of administration and redundancy of professional animal health personnel have made also oral use popular. As it was not known whether the different ivermectin administrations were of equal therapeutic value, the antiparasitic efficacy of different ivermectin formulations were in this study compared against warbles, *Hypoderma tarandi* larvae, throat bots, *Cephenemyia trompe* larvae, and gastro-intestinal nematodes in the Kaamanen Experimental Reindeer Herd. Besides ivermectin, also the efficacy of moxidectin and doramectin was evaluated, the latter, however, only against warbles and throat bots.

This study is obviously the first to compare the antiparasitic efficacy and pharmacokinetics of different administration methods of ivermectin in reindeer, and to investigate the endectocidal efficacy of moxidectin and doramectin in reindeer. Furthermore, this is the first time that throat bots have been reliably demonstrated in live animals.

While all ivermectin administration regimes (sc injection 200 µg/kg, oral paste or mixture 200 µg/kg, and pour-on 500 µg/kg) had 100% efficacy against warbles and throat bots, the nematocidal efficacy of injection was clearly matchless. From the different endectocides tested, ivermectin remains as the drug of choice, but doramectin is equal regarding warbles and throat bots. Nematocidal efficacy of doramectin in reindeer has not been examined yet. The nematocidal efficacy of moxidectin appears roughly similar to that of ivermectin, but its only moderate efficacy against warbles and throat bots makes moxidectin unsuitable for endectocidal treatment of reindeer.

The difference in antiparasitic efficacy of different ivermectin preparations is explained by pharmacokinetics; the plasma concentration following sc injection is clearly higher and longer-lasting than following either oral or pour-on administration.

To find out if timing of endectocide treatment is crucial to its efficacy, groups of reindeer hinds were ivermectin treated (oral mixture) in September, December, or February, respectively. No difference in antiparasitic efficacy or animal performance could be seen between the treated groups.

Because results from some earlier experiments indicated that antiparasitic treatment of reindeer calves during the summer might increase their growth leading to higher slaughter weights in autumn/winter, a field trial was arranged at two reindeer herding co-operatives. Groups of reindeer calves were either treated with ivermectin or left untreated in early July with the idea that the persistent effect of ivermectin might prevent parasitic infections perhaps for weeks. No difference could be seen in the slaughter weights of treated and untreated calves, and only partial prevention of warble infection. Therefore, the summer treatment does not appear feasible.

It looks clear that ivermectin treatment of reindeer should be given as sc injection, other ivermectin applications waste the drug; orally applied ivermectin apparently goes mostly into the dung, which raises ecological concern. Waste of the drug leads to underdosage, which is known to favour the rise of antiparasitic resistance in nematodes. It is probably better not to treat than to underdose.

Yhteenveto

Maapallon pohjoiskalotilla on liki 4 miljoonaa puolikesyä poroa, ja poro on mm. saamelaiskulttuurin tärkeä perusta. Työttömyyden vaivaamassa Pohjois-Suomessa noin 1800 perhettä saa merkittävän osan toimeentulostaan porotaloudesta. Suomessa porojen loislääkityksestä on tullut erittäin yleistä, noin 80% poroista lääkittää nykyään vuosittain. Lääkitys aloitettiin 1970-luvun loppupuolella kiiliaistoukkia vastaan (kurmu ja saulakka) orgaanisilla fosforiyhdisteillä. 1980-luvun alkupuolelta alkaen on käytetty ivermektiiniä, joka on rakenteeltaan ns. makrosyklinen laktoni ja vaikutukseltaan ns. endektosidi, tehoten sekä (eräisiin) sisä- että ulkoloisiin.

Lääkityksen tarkoituksena on auttaa eläimiä selviämään talvesta ja tuottamaan terveitä vasioja, ja siten parantaa porotalouden kannattavuutta. Ivermektiinilääkitys on annettu enimmäkseen ihonalaisena ruiskeena, mistä juontuu lääkityksestä joskus virheellisesti käytetty nimitys, «kurmurokotus», mikä sana on harhaanjohtava ja sitä on siksi ehdottomasti syytä välttää. Ihonalaisen ruiskeen lisäksi ivermektiiniä on annettu myös suun kautta, koska tämä on annostelutapa, jonka poromies voi itsekin suorittaa.

Koska ivermektiinin eri annostelutapojen loislääkinnällisen tehon eroja ei tunnettu, tässä työssä verrattiin niiden vaikutusta kurmuihin, saulakoihin ja ruuansulatuskanavan sukkulamatoihin Paliskuntain yhdistyksen Kaamasen koetarhalla. Ivermektiinin lisäksi myös moksidektiinin ja doramektiinin tehoa selvitettiin, jälkimmäisen tehoa tosin ainoastaan kurmuihin ja saulakoihin.

Tämä lienee ensimmäinen eri tavoilla annostellun ivermektiinin tehon ja farmakokinetiikan vertailu porolla. Tämä on myös ensimmäinen julkaistu tutkimus moksidektiinin ja doramektiinin endektosidisesta tehosta porolla. Lisäksi tämä on ensimmäinen julkaistu selostus saulakoiden osoittamisesta luotettavasti elävistä poroista.

Kaikki ivermektiinin eri annostavat (ihonalainen ruiske annoksella 200 µg/kg, suun kautta annettu pasta tai mikstuura samalla annoksella 200 µg/kg ja selälle kaadettava ns. «pour-on» annoksella 500 µg/kg) olivat 100% tehokkaita kurmuja ja saulakoita vastaan. Ihonalainen ruiske antoi kuitenkin selvästi parhaan tehon ruuansulatuskanavan sukkulamatoja vastaan. Kokeilluista eri lääkeaineista ivermektiini on edelleen suositeltavin, mutta doramektiinilläkin on hyvä teho kurmuja ja saulakkaa vastaan. Moksidektiini vaikuttaa ivermektiinin veroiselta sukkulamatoja vastaan, mutta sen teho kurmuun ja saulakkaan ei ole erityisen hyvä, mikä estää moksidektiinin soveltumisen poron loislääkintään endektosidina.

Eri ivermektiinivalmisteiden tehoerot selittyvät farmakokinetiikalla; ihonalaisen ruiskeen aiheuttama lääkeainepitoisuus veriplasmassa on selvästi korkeampi ja pitempikestoinen kuin annettaessa lääke suun kautta tai selälle kaadettuna.

Lääkityksen ajoituksen merkityksen selvittämiseksi vaadinryhmiä lääkittiin ivermektiinimikstuuralla (suun kautta) joko syyskuussa, joulukuussa tai helmikuussa. Lääkityksen tehossa, eläinten painon kehityksessä tai vasojen syntymäpainoissa näiden lääkitysryhmien välillä ei havaittu eroja.

Koska eräät aiemmat tulokset viittasivat siihen, että kesällä suoritettu vasojen loislääkitys voisi lisätä niiden kasvua johtaen korkeampiin teuraspainoihin, kokeiltiin kahdessa paliskunnassa vasojen lääkitystä ivermektiinillä korvamerkinnän yhteydessä heinäkuun alussa. Lääkittyjen ja lääkittämättömien vasojen teuraspainojen välillä ei ollut eroja. Lääkitys ei estänyt kurmutartuntaakaan täydellisesti. Kokeen perusteella vasojen kesälääkintä ei ole mielekäästä.

Ainoa suositeltava ivermektiinin antotapa porolle on ihonalainen ruiske. Muut lääkkeenantotavat haaskaavat vaikuttavaa ainetta. Suun kautta annettuna ivermektiini sitoutuu suurimmalta osaltaan pötsin sisältöön ja joutuu sen mukana ulosteisiin imeytymättä elimistöön. Lääkkeen joutuminen suoraan ulosteisiin on ympäristön kannalta huolestuttavaa, koska ivermektiinin hyönteismyrkkyvaikutus voi olla lannan hajoittajille tuhoisa. Koska lääke ei joudu loisten ulottuville toivottuina pitoisuuksina, sekä suun kautta annettu että «pour-on» -lääkitys johtavat käytännössä aliannosteluun huolimatta sinällään riittävästä vaikuttavan aineen määrästä. Aliannostus on yksi tärkeimmistä tekijöistä, jotka edistävät loislääkkeelle vastustuskykyisten sukkulamatojen syntyä. Yleensä lienee parempi jättää loislääkittämättä kuin aliannostella.

Čoahkkáigeassu

Eanaspáppa davviosiin ellet lagabui 4 miljovna beallelojes bohcco. Boazu ja boazodoallu mearkkašeaba ollu omd. sámekultuvrii. Davvi-Suomas, gos lea ollu bargguhivuohta, sullii 1800 bearraša ožžot mávssolaš oasi áigáiboadusteaset boazodoalus. Bohccuid dálkkodeapmi parasitaid vuostá lea dáid áiggiid hui dábalaš Suomas, sullii 80% bohccuin dálkkoduvvojit dál jahkásaččat. Dálkkodeapmi álggahuvvui 1970-logus gurmáid ja sávlagiid vuostá orgánalaš fosforovttastusaiguin. 1980-logu álggu rájes lea boahán atnui ivermektiidna, mainna sáhtá hehttet muhtun sis- ja olgoparasitaid njoammuma bohccui.

Dálkkodeami ulbmilin lea veahkehit bohccuid ceavzit badjel dálvvi ja buvttadit dearvvas misiid ja ná buoridit boazodoalu gánnáheami. Ivermektiidna cirgguhuvvo dábalaččat liikki vuollai, man sivas dan lávejit gullot muhtumin boastut gohčodeamen «gurbmáboahkoheapmin». Liikkivuoláš dálkkodeami lassin ivermektiinna lávejit addit maiddá njálbmeráigge, ja dát dálkkodanvuohki lea dakko bokte buorre, ahte boazodoalli sáhtá iešge dan dahkat.

Dát dutkan čadahuvvui Bálgosiid Ovtastusa Gápmasa dutkangárddis. Dutkamis veardiduvvui ivermektiinna sierra addinvugiid váikkuhanbeaktilvuohka gurmáide, sávlagiidda ja biebmossuddadanoali suhkkolmáduide. Ivermektiinna lassin maiddá moksidektiinna ja doramektiinna beaktilvuohka čilgejuvvui, manjibu beaktilvuohka gal dušše gurmáide ja sávlagiidda.

Dát lea várra vuosttas veardádallan ivermektiinna sierra addinvugiid beaktilvuodas bohccui. Dát lea maiddá vuosttas olggosaddojuvvon dutkan moksidektiinna ja doramektiinna beaktilvuodas. Dasa lassin dát lea vuosttas olggosaddojuvvon čilgehus, mo sáhtá luottehahti láhkai oaidnit ahte leatgo bohccos sávlagat.

Buot ivermektiinna addinvuogit ledje 100% beaktilat gurmáid ja sávlagiid vuostá. Liikkivuoláš cirgguheapmi lei goittot čielgasit beaktileamos biebmossuddadanoali suhkkolmáduid vuostá. Ivermektiidna lea ainge dat dálkkasávnas, man gánnáha ovddimus geavahit parasitadálkkodeamis, muhto doramektiidnaga váikkuha bures gurmáid ja sávlagiid vuostá. Moksidektiidna orru leamen seamma beaktil go ivermektiidna suhkkolmáduid vuostá, muhto dan váikkuhus gurmáid ja sávlagiid vuostá lea dušše gaskageardán.

Sierra ivermektiidnabuktagiid beaktilvuodaearuid sáhtá čilget farmakokinetihkain: liikkivuoláš cirggastaga dagahan dálkkasávnasdoallu lea varraplasmas mealgat alit ja guhkitáigásaš go jos dálkkas addojuvvo njálbmeráigge dahje leikejuvvo čielggi ala. Go čilgejuvvui goas dálkkas galgá addojuvvot, de dade várás áldočorragat dálkkoduvvojedje ivermektiinnain njálbmeráigge juogo čakčamánuš, juovlamánuš dahje guovvamánuš. Dálkkodeami beaktilvuodas, ealliid deattu molsašuddamis dahje misiid šaddandeattuin eai gávdnon earut máinnašuvvon dálkkodanvugiid gaskkas.

Go muhtun ovddit dutkamat orro ča jeheamen ahte geassit čadahuvvon misiid parasitadálkkodeapmi sáhtá lasihit daid njuovvandeattu, de guovtte bálgosis geahčaledje misiid dálkkodeami ivermektiinnain mearkunáigge suoidnemánu álggus. Dálkkoduvvon ja dálkkokeahtá báhcán misiid njuovvandeattuid gaskkas eai lean earut. Ja ii dálkkodeapmige hehtten ollásit gurmáid šaddama bohccui. Dán geahčaleami vuodul orru nu, ahte misiid ii gánnát dálkkodit geassit.

Áidna vuogas ivermektiinna addinvuohki bohccui lea liikkivuoláš cirggastat. Eará addinvuogit háskkidit váikkuheaddji ávdnasa. Njálbmeráigge attedettiin ivermektiidna njammasa eanaš guomočoavjji sisdollui ja gártá das baikii iige njammas albmaláhkai organismii. Dálkasa gártan njuolgga baikii lea birrasa dáfus hui fuoneš ášši, dasgo ivermektiinna divremirkováikkuhus sáhtá leat baikka háddjejeaddjiide hui váralaš. Go dálkasa váikkuhus ii čuoze parasitaid dakkár doaluid mielde go lei doivojuvvon, de njálbmeráigge attedettiin ja čielggi ala leikedettiin váikkuheaddji dálkkasávnas lea álo menddo uhccán parasitaid jávkadeami várás. Dát fas dagaha dan, ahte šaddet parasitadálkasi immuna suhkkolmáhtomáddodagat. Mángii lea várra juoba buoret guoddit ollásit dálkkokeahtá go dálkkodit nu, ahte váikkuheaddji dálkkasávnas gártá menddo uhccán organismii parasitaid jávkadeami várás.

Sammendrag

Det finnes alt i alt nesten 4 millioner halvdomestiserte reinsdyr, og reinen er ett viktig grunnlag for flere folkegrupper, bl.a. for samekulturen. I Nord-Finland, der det er stor arbeidsledighet, får ca 1800 familier en viktig del av sysselsettingen fra reindriften. I Finland har antiparasittbehandling av rein blitt svært vanlig; ca 80% av reinsdyr blir behandlet årlig. Behandlingen ble startet på slutten av 1970-tallet med organofosfater, og siden tidlig på 1980-tallet har man brukt ivermektin, som er en makrosyklisk lakton, og som virker endektosidisk, dvs. har effekt både mot (en del) endo- og ektoparasitter.

Hensikten med behandling er å fremme dyrs overlevelse gjennom vinteren og produsere levedyktige og gode kalver, og på den måten øke lønnsomheten i reindriften. Mest har man gitt ivermektin som injeksjon under huden, som har ført til at behandlingen ofte har feilaktig blitt kalt «vaksinering». Foruten som injeksjon, har ivermektin også blitt gitt oralt, fordi det er en administreringsmåte som reineieren selv kan foreta.

Effekten av de ulike appliseringsformene av ivermektin mot bremselarver og nematoder ble i dette arbeidet sammenlignet i Kaamanen forsøksflokk i Inari i finske Lappland. I tillegg til ivermektin ble også effekten av moksidektin og doramektin undersøkt, doramektin bare mot bremselarver.

Avhandlingen innbefatter dermed de første sammenliknende undersøkelser av antiparasitteffekten og farmakokinetikken av forskjellige måter å administrere ivermektin til rein. Dessuten presenteres de første publiserte resultater fra effektstudier av moksidektin og doramektin i reinsdyr og den første beskrivelsen av en pålitelig måte å påvise svelgbremselarver hos levende vertsdyr.

Alle de forskjellige måter å gi ivermektin (injeksjon 200 µg/kg, oral pasta eller mikstur 200 µg/kg, og perkutan s.k. «pour-on» 500 µg/kg) hadde 100% effekt mot bremselarver. Dertil hadde injeksjon helt klart beste effekt mot mage-tarm-nematoder. Av de forskjellige endektosider er ivermektin fremdeles den eneste å anbefale, men også doramektin er svært effektiv mot bremselarver. Dets nematoside effekt har ikke blitt undersøkt i rein. Moxidektin synes å være like effektiv som ivermektin mot nematoder, men dets effekt mot bremselarver er ikke særlig god, og derfor passer ikke moxidektin som et parasittmiddel for rein.

De forskjellene, som finnes i effekten av de ulike ivermektinpreparater, kan forklares med farmakokinetikk; plasmakonsentrasjoner er klart høyere og mer langvarig etter injeksjon enn ved oral eller «pour-on» administrering.

For å finne ut om behandlingstidspunktet har stor betydning, ble simlegrupper behandlet oralt med ivermektinmikstur enten i september, desember eller i februar. Det ble ikke funnet forskjell i antiparasitteffekten, heller ikke i vektutvikling eller fødselsvekter av kalver mellom de behandlede grupper.

Enkelte tidligere resultater hadde indikert at antiparasittbehandling av ungalver midt på sommeren kunne øke tilveksten og lede til høyere slaktevekter. Derfor ble kalver i to reinbeitesdistrikter (paliskunta) behandlet med ivermektin i forbindelse med øremerking i begynnelsen av juli. Det ble ikke registrert forskjell i slaktevektene mellom ivermektinbehandlede og ubehandlede kalver. Heller ikke ble hudbrensinfeksjon helt forhindret. Av disse grunnene er sommerbehandlingen av kalvene unødvendig.

Hovedkonklusjonen er at injeksjon er den eneste administreringsmåten av ivermektin som er å anbefale, andre måter sløser virkestoff. Ivermektin gitt oralt blir mest adsorbent i vomineholdet, og går siden direkte i faeces uten å bli absorbert i kroppen. At virkestoffet går direkte i møkk, kan være miljømessig bekymrende. Både oral og «pour-on» applisering leder i praksis til underdosering, ved at virkestoffet ikke når parasittene i ønskede konsentrasjoner selv om man bruker doser som er like store (oral) eller større («pour-on») enn det man anbefaler til injeksjon. Underdosering er en av de mest kjente faktorene som bidrar til antiparasittmiddelresistens i nematoder. Man bør derfor heller la være å behandle enn å underdosere.

List of original publications

This dissertation is based on the following original publications referred to in the text by their Roman numerals:

- I. Oksanen, A., Nieminen, M., Soveri, T. & Kumpula, K. 1992. Oral and parenteral administration of ivermectin to reindeer. - *Veterinary Parasitology* 41: 241-247.
- II. Oksanen, A., Soveri, T. & Nieminen, M. 1992. Fibre-optical pharyngoscopy for diagnosing throat bots in the reindeer. Short Communication. - *Bulletin of the Scandinavian Society for Parasitology* 1992; 2: 30-32.
- III. Oksanen, A., Nieminen, M. & Soveri, T. 1993. A comparison of topical, subcutaneous and oral administrations of ivermectin to reindeer. - *Veterinary Record* 133: 312-314.
- IV. Oksanen, A., Norberg, H., Nieminen, M. & Bernstad, S. 1995. Influence of route of administration on the plasma concentrations of ivermectin in reindeer. - *Research in Veterinary Science* 58: 286-287.
- V. Oksanen, A. & Nieminen, M. 1998. Moxidectin as an endectocide in reindeer. - *Acta Veterinaria Scandinavica*. 39: 469-475.
- VI. Oksanen, A. & Nieminen, M. 1996. Larvicidal effectiveness of doramectin against natural warble (*Hypoderma tarandi*) and throat bot (*Cephenemyia trompe*) infections in reindeer. - *Medical and Veterinary Entomology* 10: 395-396.
- VII. Oksanen, A. 1996. Influence of timing of endectocidic antiparasitic treatment on its efficacy in overwintering reindeer. - *Rangifer* 16: 147-150.
- VIII. Oksanen, A., Norberg, H. J. & Nieminen, M. 1998. Ivermectin treatment did not increase slaughter weight of first-year reindeer calves. - *Preventive Veterinary Medicine* 1998; 35: 209-217.

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Abbreviations

ANOVA	Analysis of variance
AUC	Area Under Curve
C _{max}	Maximum concentration
DRM	Doramectin
endectocide	Macrocyclic lactone antiparasitic against both (some) endoparasites and ectoparasites
epg	Eggs per gram of faeces
FEC	Faecal egg count
GABA	Gamma-amino butyric acid
IVM	Ivermectin
lpg	Larvae per gram of faeces
ML	Macrocyclic lactone
MXD	Moxidectin
po	<i>Per os</i>
sc	Subcutaneous
s.e.m.	Standard error of the mean
t _{max}	Time when maximum concentration is reached after drug administration

Introduction

Reindeer, the circumpolar cervid

The reindeer genus *Rangifer* comprises only one species, *R. tarandus* living in the northern hemisphere, both in the Palearctic (Eurasian) and Nearctic (American) areas (Banfield, 1961). It inhabits most of the circumpolar land areas not covered by permanent ice. The southernmost reindeer (apart from those introduced to the southern hemisphere) graze in China (50 °N) and the northernmost on Svalbard, Greenland and arctic islands of Canada, even north of 80 °N. According to current systematics, there were 12 subspecies of *R. tarandus*, but two of them are now extinct (in Nieminen, 1994). There is not full agreement about the number of subspecies, other authors (e.g. Tyler & Røed, 1993) count 7 subspecies. The most important reasons for the evolution of the subspecies have apparently been the separation of the Asian and American continents and the repeated glacial periods (in Nieminen, 1994). The Nearctic wild reindeer is called caribou.

The semi-domesticated reindeer descends from the wild Eurasian mountain or tundra reindeer *R. t. tarandus*. There are still some 33 000 wild mountain reindeer in southern Norway, where they are important game animals (Skogland, 1994). As late as in 1970 it was estimated that there were also 22 000 wild reindeer on the Kola peninsula, but the number decreased to 2700 in 1984 (in Syroechkovskii, 1995). The semi-domesticated reindeer has probably also genes from the wild forest reindeer, *R. t. fennicus*, with which it readily cross-breeds. Some years ago, there were about 1 000 wild forest reindeer in Finland, partly in a close neighbourhood of the reindeer husbandry area (Kojola, 1995), but the population is growing. A relatively recent estimate of the population of this subspecies in Russian Karelia is 6 000 to 10 000 animals (in Nieminen, 1993a). The wild reindeer has always been a popular game animal wherever it shares habitat with humans. Reindeer hunt was practised in central Europe before the last Ice Age, and in Norway there is evidence of hunt 10 000 to 12 000 years ago.

The semi-domesticated reindeer

The reindeer has been crucial to the Saami and other northern peoples and cultures, enabling the settlement of the barren arctic and subarctic regions. The first report on European reindeer husbandry is obviously from AD 892, when the Norwegian chieftain Ottar informed King Alfred of

England that he owned 600 reindeer, six of which were valuable decoy animals used to lure wild reindeer. Reindeer husbandry obviously developed from such hunt with decoy animals (in Vorren & Manker, 1976; Skjennberg, 1984).

The contemporary estimate of the total *Rangifer* population of the world is nearly 8 million animals, half of them semi-domesticated (Staaland & Nieminen, 1993). About 20% of the semi-domesticated reindeer are in Fennoscandia (Finland, Sweden and Norway) and 75% in Russia, and the rest in North America and Greenland, with some thousand wild descendants of released semi-domesticated reindeer on Iceland, South Georgia (54°30'S, 37°0'W) and Kerguelen (48°15'S, 69°10'E). Small-scale reindeer herding is also practised in Scotland and Japan (in Nieminen, 1993b).

The main reindeer product is meat, but also hides possess a considerable income in Finland (Nieminen, 1992). In Russia reindeer are still important draught animals, and they are also milked and used in riding at some locations (Nieminen, 1995). Reindeer racing is becoming popular in Fennoscandia, so much so that doping tests have been introduced (Nieminen *et al.*, 1997). Velvet antlers constitute the major reindeer product in Alaska (Nieminen & Muhonen, 1996).

Reindeer calves are born mostly in May and early June with a body weight of 4-7 kg, and grow fast during the summer, commonly reaching body weight of 50 kg or more in September-October. Reindeer seldom deliver twins. In many areas, calves are ear-marked in midsummer. To do it, the flock must be rounded up. The next round-ups take place in autumn or winter, when animals are selected for breeding, and others are slaughtered. Those selected to live are often treated with antiparasitics (Kemppainen *et al.*, 1997).

Finnish co-operative reindeer husbandry

The Finnish reindeer husbandry organisation was founded in the 18th century. The basic unit, the reindeer herding co-operative, is called *paliskunta*, which name was first used in the beginning of the 19th century. Reindeer are owned by individual herders within a co-operative, but the pastures are common. The co-operatives are mostly separated from each other by means of fences. Presently there are 56 co-operatives, 40 in Lapland and 16 in the province of Oulu. The Finnish *paliskunta* has counterparts in Sweden, *sameby*, and in Norway, *reinbeitedistrikt*, or *siida*. The organisation structures differ, as in the Scandinavian countries the level of co-operation is lower, and reindeer

husbandry is limited to the indigenous Saami people. In Finland anybody (European Economic Area citizens) living within the reindeer husbandry area and being a member of the local co-operative has a legal right to own reindeer (Huttu-Hiltunen, 1993). In Finland, there are 6800 reindeer owners, and about 800 families live primarily on reindeer husbandry, but another 1000 get a considerable part of their living from reindeer (Anon., 1998). The reindeer husbandry area now comprises 115 000 square kilometres, or slightly over one third of the country.

The co-operative reindeer herding system has proved flexible and has continuously adapted new methods to intensify production. The total number of reindeer in Finland was 37 000 in 1845 (in Nieminen, 1993a). During the first half of the 1970's the number oscillated between 100 000 and 150 000. Because of the launch of new techniques, such as calf slaughter, winter supplementary feeding, and antiparasitic treatment, as well as the use of motorised herding, the amount increased rapidly, reaching 200 000 to 250 000 during the latter half of the 1980's. Between 1970 and 1976, the annual number of animals slaughtered averaged 38 000. It peaked in 1990-1991, when 160 000 reindeer were slaughtered. After that, both the overwintering population and the amount slaughtered have diminished. During 1996-1997, 202 000 reindeer were counted alive, 28 000 of which were calves. Eighty-eight thousand reindeer were slaughtered, whereof 61 000 calves (Anon., 1998). While calves contributed to less than one third of the slaughter reindeer in the early 1970's, the current proportion is about three fourths (Kemppainen *et al.*, 1997).

Carrying capacity of the Finnish reindeer pastures was clearly exceeded during several decades (Kojola & Helle, 1993; Kumpula *et al.*, 1997). It has been extended with increased supplementary feeding and pen-feeding where winter pastures are scarce (Helle & Kojola, 1993; Kemppainen *et al.*, 1997; Nieminen *et al.*, 1998). In addition, the increased slaughter of calves keeps the overwintering population low. To minimise parasite-induced damage to the condition of the animals, antiparasitic treatment is used. This may indirectly help in keeping the overwintering breeding stock as small as possible. About 80% of overwintering reindeer are treated yearly with ivermectin (Anon., 1993). Future challenges are in sustainability; balancing reindeer husbandry and its productivity needs with the carrying capacity of the pastures, not forgetting the other needs of the

ground, e.g. conservation, forestry, agriculture and tourism.

PARASITE FAUNA OF THE REINDEER AND ANTIPARASITIC MEASURES

A parasite is a symbiont living on the cost of the other counterpart of the symbiosis, the host. Reindeer harbour a variety of different parasites (see Halvorsen, 1986). Although viruses, many bacteria and fungi are definitively parasitic, they are not handled with in this thesis. So, the parasites here are (invertebrate) animals living of the reindeer. Furthermore, those not practically controllable with current macrocyclic lactone (ML) endectocides are not discussed at all. ML endectocides have efficacy against nematodes and arthropods, which phyla contain many important reindeer parasites. It is worth specially noticing that ML endectocides do not have efficacy against cestodes, such as *Echinococcus* and *Moniezia* tapeworms, and trematodes, such as the *Paramphistomum* rumen fluke and liver flukes. The knowledge on the efficacy of ivermectin against reindeer parasite species is discussed in a later chapter (page 27), and because other ML endectocides are newer products, there is no former literature on the use of them in reindeer.

Losses estimated to be due to reindeer parasites (gain of treatment)

It is perhaps principally erroneous to discuss parasite-induced losses in reindeer, as the parasites certainly belong to the ecosystem the reindeer live in, almost like weather and vegetation, and are not so easily separable additions. It is therefore better to debate in terms of possible gains caused by antiparasitic treatment. In older literature, however, attempts to estimate the costs of parasitism were often made. Nordkvist (1967) estimated warbles and throat bots to consume 15-20% of the reindeer production income in Sweden, and Saval'ev (1968) approximated warbles alone to reduce the income of the Soviet reindeer husbandry by 25-30%. Thinking about such high losses of production, control measures might easily appear worthwhile. There is, however, very little scientific evidence that organophosphate treatments would have improved the survival or weight gain of reindeer, although several experiments showed a high degree of efficacy against warbles and throat bots (Nordkvist 1967; Klement'eva, 1975; Nieminen *et al.*, 1980; Persen *et al.*, 1982). In one experiment, weight loss during winter was higher in famphur treated calves than in untreated ones, but the

subsequent higher weight gain during summer compensated the winter weight loss, leading to slightly higher mean slaughter weights in treated animals the next autumn (Persen *et al.*, 1982). Parasite weight might at least partly have been responsible for the higher live weight of untreated animals in the spring. A single full-grown 3rd stage warble larva weighs 1.6 to 1.7 g (Nilssen, 1997a). Nordkvist (1967) calculated that a normal warble infection could make up a larval mass of about 500 g per reindeer. The probably higher value of intact hides from reindeer treated during the previous years might have increased the profitability of organophosphate treatment.

Later, using ivermectin, Nordkvist *et al.* (1984) showed significantly lower mean live weight loss (10.2 kg compared with 14.0 kg) in treated than in non-treated reindeer calves during winter. In another trial, a significant increase in mean live weight gain of about 3 kg was seen during the subsequent year in treated calves as compared to non-treated ones (Heggstad *et al.*, 1986).

In one trial, antiparasitic treatment with ivermectin increased antler symmetry, which was speculated to be related with reproductive success (Folstad *et al.*, 1996).

Summer treatment of reindeer calves with ivermectin or luxabendazole (broad-spectrum benzimidazole anthelmintic with efficacy against nematodes, cestodes and trematodes) has in two small trials increased the weight gain of reindeer calves before the slaughter season (Oksanen & Nieminen, 1995; Oksanen *et al.*, 1996). This indicates that subclinical parasitism may be a growth-limiting factor to reindeer calves, at least if the infection pressure is high.

Parasite species

Nematodes

Nematodes are commonly considered the most important parasites of domestic ruminants. In cattle, sheep and goats, gastrointestinal nematodes can cause even fatal disease or, more commonly, subclinical infection that leads to impaired production (Urquhart *et al.*, 1987). The most important gastrointestinal nematodes are those of the abomasum (*Ostertagia* spp., *Haemonchus* spp.) but also nematodes of the small intestine (*Trichostrongylus* spp., *Nematodirus* spp., *Cooperia* spp.) are regarded as important pathogens in some areas (Soulsby, 1982). The other important group of parasitic nematodes in domestic ruminants is the *Dictyocaulus* spp. lungworms. In farmed red deer (*Cervus elaphus*), *Dictyocaulus* lungworms are

considered the most important parasites (Watson & Charleston, 1985), but also abomasal nematodes may cause clinical disease (Connan, 1991).

Brainworm

A lot of nematode species are known also from the reindeer, but most of them have usually been regarded as rather harmless. The most widely recognised pathogen is probably the brainworm *Elaphostrongylus rangiferi*, which is blamed for severe outbreaks of meningoencephalitis after warm and rainy summers (Handeland & Slettbakk, 1994). Reindeer brainworms have been studied extensively (e.g. Bakken & Sparboe, 1973; Halvorsen, 1986; Handeland & Norberg, 1992; Hemmingsen *et al.*, 1993; just to name a few). The life cycle of the brainworm is heteroxenous with snails as intermediate hosts and reindeer as definitive host. The reindeer brainworm can also infect moose (Stéen *et al.*, 1997), sheep and goats (Handeland, 1991; Handeland & Sparboe, 1991; Handeland & Skorping, 1992).

Gastro-intestinal nematodes

Reindeer are also known to harbour several species of abomasal and intestinal nematodes (Bye & Halvorsen, 1983; Bye, 1987; Bye *et al.*, 1987; Fruetel & Lankester, 1988; Korsholm & Olesen, 1993), but so far there is only little evidence of their clinical importance (Christensson & Rehbinder, 1975; Rehbinder & Christensson, 1977; Rehbinder & von Szokolay, 1978). However, Arneberg *et al.* (1996) clearly showed that abomasal nematodes depress food intake in reindeer during late winter. Reindeer calves, born mostly in May, pick up infective stages of gastro-intestinal parasites soon after their birth and harbour patent nematode infections as early as late June or early July (Oksanen *et al.*, 1990).

The most important gastro-intestinal nematodes are those in the abomasum (Fruetel & Lancaster, 1988), but reindeer calves have also *Nematodirus* and/or *Nematodirella* nematodes of the small intestine (Bye, 1987; Oksanen *et al.*, 1990). The reindeer specific species are *Nematodirus tarandi* and *Nematodirella longissimespiculata*, but also other species primarily from other hosts may parasitise reindeer (Fruetel & Lankester, 1988). Other intestinal nematodes are *Capillaria* sp. (Christensson & Rehbinder, 1975; Rehbinder & Christensson, 1977; Nordkvist *et al.*, 1983, 1984) and *Trichuris* sp. (in caribou, Fruetel & Lancaster, 1988). The life cycles of intestinal nematodes are not well-known, but the transmission is probably direct. It is known that the eggs of *Nematodirus*

battus of lambs develop further and hatch only after winter, but eggs of other species of the genus may hatch during the summer they were produced (Urquhart *et al.*, 1987). Thus, *N. battus* from lambs produce eggs that become infective for the lambs of the subsequent year. It is not known whether *N. tarandi* follow a pattern similar to *N. battus* or not, but the short summer of the Arctic might make that strategy beneficial.

Pinworms of the genus *Skrjabinema* live in the caeca of ruminants. Females deposit eggs on the perianal skin, where they drop off and can be with faecal samples. The parasites are not considered pathogenic (Soulsby, 1982), but are occasionally observed in sheep and goats (Borgsteede and Dercksen, 1996). In one experiment, immature and adult *Skrjabinema ovis* were present in two ivermectin treated goats (DeVaney *et al.*, 1992). One species of the genus, *S. tarandi*, is known to occur in reindeer, also in Finland (S. Nikander, unpublished). Eggs of the genus are easily recognised because of their highly asymmetrical shape.

Abomasal nematodes

The most common abomasal nematode species is the reindeer specific *Ostertagia gruehneri* (Bye & Halvorsen, 1983; Bye, 1987; Nikander, 1988; Fruetel & Lancaster, 1988). Another reindeer specific species, *O. arctica*, is now considered the less common morphotype of *O. gruehneri* (Lichtenfels *et al.*, 1990). Moreover, many species that principally parasitise other cervids or domestic ruminants have been found in reindeer abomasum (Pryadko, 1976; Bye & Halvorsen, 1983; Fruetel & Lancaster, 1988; Korsholm & Olesen, 1993). The life cycle of *O. gruehneri* is obviously similar to that of other members of the genus. Seasonal inhibition, as known in *Ostertagia* spp. from domesticated ruminants in temperate areas (e.g. Michel *et al.*, 1974; Thomas & Waller, 1979) and also from deer (Connan, 1991, 1997; Belem *et al.*, 1993), has also been observed in reindeer (Nordkvist *et al.*, 1984). The long arctic winter obviously makes this strategy meaningful for parasite (and host) survival. It has been found that the abundance of abomasal nematodes in reindeer calves may be considerably lower than that of adult reindeer (Bye & Halvorsen, 1983; Bye, 1987), which is in discrepancy with what is known from domestic ruminants. The importance of milk as a source of nutrition to reindeer calves may explain this finding (see Nieminen, 1994). An interesting and surprising abomasal nematode species found in the wild polar Svalbard reindeer *Rangifer tarandus*

platyrhynchus (Bye & Halvorsen, 1983; Bye *et al.*, 1987) is *Marshallagia marshalli*, the distribution of which is generally considered to be much more southern in domesticated ruminants (Soulsby, 1982; Barth, 1991).

Lungworm

Lungworm infection is common in reindeer and may cause serious disease (Kummeneje, 1977; Dau, 1981; Holmström *et al.*, 1989). The causative species was earlier identified as *Dictyocaulus viviparus*, that of bovines, but now the reindeer species is most often referred to as *D. eckerti* (Skrjabin *et al.*, 1971; Rahko *et al.*, 1992; Nikander & Saari, 1993).

Vector-transmitted nematodes

Besides the nematodes infecting reindeer orally, there are several known or suspected arthropod vector -transmitted nematode parasite species in reindeer. *Onchocerca tarsicola* was commonly detected (30%) in tibiotarsal or radiocarpal regions of limbs of 407 Finnish reindeer. The worms were most often found in flat swellings or nodules of connective tissue in membranes surrounding the tendons of the tibiotarsal and radiocarpal joints (Bylund *et al.*, 1981). The parasite is transmitted by simuliids (Schulz-Key & Wenk, 1981). *Lappinema auris* is a nematode which induces the formation of large fibrotic nodules on the auricles of reindeer. Males of the parasite are unknown, and parthenogenetic reproduction is suspected (Bain & Nikander, 1983). The species has become rare, perhaps because of endectocide treatment (Nikander, 1992). Subcutaneous parasitic nodules in the muzzle of reindeer were thought perhaps to be caused by an *Onchocerca* nematode (Lisitzin, 1964). Both *O. tarsicola*, *E. rangiferi* and *Setaria tundrae* were found in visceral granulomas of Swedish reindeer (Rehbinder *et al.*, 1979; Rehbinder, 1990). In Alaska, *Setaria* of the reindeer has been identified as *Setaria yehi*. The parasite has been associated with subclinical chronic peritonitis (Dieterich & Luick, 1971).

Nematocidal treatment

Because the brainworm is considered a dangerous pathogen, several anthelmintics have been experimented against it. No efficacy was seen following treatment with chlorophos, dithiazine phosphate, phosphamide or tetramisole, while phenothiazine temporarily reduced their reproduction (Smirnov, 1976). In one experiment, reindeer infected with *E. rangiferi* were treated daily for 10 days with mebendazole given at 6

mg/kg bodyweight in feed. This treatment eliminated brainworm larval production for at least 43 days, but in another group of reindeer a single dose of mebendazole at 40 mg/kg bodyweight did not remove these larvae (Rehbinder *et al.*, 1981). In another trial, both mebendazole and fenbendazole at 6 mg/kg/day for 10 days had high efficacy against *E. rangiferi* (Nordkvist *et al.*, 1983). Oral tetramisolum at 10 mg/kg 2 or 3 times a year has been empirically observed to eliminate *Dictyocaulus* and *Trichostrongylus* species from reindeer herds (Kurkela & Kääntee, 1978).

Arthropods

Both insects, arachnids and pentastomids include parasites of reindeer.

Insects

Insect parasites of reindeer, excluding harassment by blood-sucking insects, include lice and oestrid flies. Sucking lice, *Solenopotes tarandi*, were originally described in Sweden (Mjöberg, 1915) and are also known from Alaska (Weisser & Kim, 1973). Biting lice, *Damalinea tarandi*, were also described in Sweden (Mjöberg, 1916), and are also known from Finland (A. Oksanen, unpublished). The pathogenic effect of lice in reindeer is unknown.

There are two oestrid fly species (Diptera: Oestridae) parasitising the reindeer, the warble fly *Hypoderma tarandi* and the throat bot fly *Cephenemyia trompe*. The imago of these flies lack mouth parts, and do not feed. Therefore, the entire nutritional needs are covered by parasitism during the larval stage (see Nilssen & Anderson, 1995b).

Warble

Larvae of *H. tarandi* are called warble fly larvae (e.g. Helle, 1980), subcutaneous gadfly larvae (Solopov, 1989), warble bots (Nilssen & Haugerud, 1995) and grub fly larvae (Nordkvist, 1967). Because of simplicity, and consistent with Dieterich & Craigmill (1990) and Verduyck (1993), they are here called just warbles, even though this word can also refer to the whole pupule formation, consisting both of the larva and host tissue reaction. In Latin, reindeer warble was earlier called *Oedemagena tarandi* (also in publications I and III), but the inclusion of the species in the genus *Hypoderma* is now generally accepted (Wood, 1987).

The life cycle of *H. tarandi* is very similar to that of other species of *Hypoderma* (e.g. *H. bovis* and *H. lineatum* of cattle). Female warble flies lay eggs on hairs of the host, especially on feet, during

the summer (Saveljev, 1968; Anderson *et al.*, 1994). The larvae hatch, crawl down the hair and penetrate the skin (Karter *et al.*, 1992). They wander in the connective tissue, and reach the subcutaneous tissue of the back, where they mature to the 3rd instar (Breyev, 1971). During the winter, they perforate the skin and breath through the hole. In spring the mature larvae emerge, drop down, bury to the ground, where they pupate, and the imago emerge about one month later (Nilssen, 1997b). The infection intensity in reindeer is often high; the average number (150-200) is some ten times higher than that of *H. bovis* and *H. lineatum* in cattle (Breyev, 1961).

Warbles are nearly ubiquitous in reindeer. Generally, just the northernmost Arctic herds, and those in the southern hemisphere, are unaffected. They are absent from Svalbard and Iceland (Skjenneberg & Slagsvold, 1968; Saval'ev, 1968; Leader-Williams, 1980; Wahburn *et al.*, 1980). In the barren ground caribou of the Canadian Beverly herd located south from 65°N, as many as 97 to 100% of animals sampled had warbles, but in the Peary caribou on the Canadian Parry Islands (75°N) only 14% were infected (Thomas & Kiliaan, 1990). A plausible explanation for the absence of warbles from the high Arctic regions is the cold climate. The free-living pupae require at 12 °C not less than 50 days to develop, while at 27 °C development could take less than 10 days (Nilssen, 1997b).

Nordkvist (1967) estimated that normally more than 95% of reindeer were infected in Sweden. In western Finnmark in northern Norway, 99.9% of 1305 reindeer hides were warbled (Folstad *et al.*, 1989). In Finland the prevalence and infection intensity of reindeer warbles were investigated in adult males, females and calves of six reindeer herding co-operatives (Helle, 1980). A general observation was that calves and males were more heavily infected than adult females, which is in agreement with the Norwegian results (Folstad *et al.*, 1989). In Finland, both prevalence and infection intensity were lowest in the southernmost co-operative located in the forest area, prevalence there in calves being from 42 to 63% and abundance (mean intensity) from 3 (s.e.m. 1) to 11 (4) during the three year study. In the northernmost co-operatives the prevalence was 87 to 100%. Abundance there varied between 23 (6) and 75 (6) larvae. Warbles were thus most common in the northernmost areas. It is possible that the flies find each other and the reindeer easier in the open terrain of the north (Helle, 1982).

Earlier, warbles were often removed mechanically by compressing them between the thumb and

forefinger in the spring. Bergman (1917) experimented with covering the back of reindeer with tar to suffocate warbles instead of the laborious compression. The results were promising, but the method never became widely used. Instead, the compression method was still utilised sporadically. Even though the procedure was laborious, Saval'ev (1968) considered it useful irrespective of other possible control measures. After compression, the warble holes could be covered with creolin emulsion (Saval'ev, 1968). Another control method of warbles and throat bots was resting the herd on wet swamps in early summertime in order to let the emerging larvae drown (Nordkvist, 1967).

Because of their specific attraction to light coloured reindeer, warble fly females were lured to land on unfolded white hides where they were easily killed, which was a task of youths (Saval'ev, 1968). Other prophylactic measures were driving the herd after calving at least 50 to 60 kilometres away from the place where the parasite larvae were shed, and not returning to the calving ground before mid September (Saval'ev, 1968). This kind of migration is considered natural to the reindeer (Folstad *et al.*, 1991). Hadwen (1926) noticed that Lapland reindeer had fewer warbles than those in Alaska, perhaps because the herds were constantly moving. He also mentioned to have seen dark sheds in Finnish Lapland that provided shelter to reindeer against all forms of insect harassment. Such a «*liemu*» shed can nowadays be seen at the *Siida* Saami museum in Inari. Also smokes have been used to repel insects during the warmest summer days (Saval'ev, 1968). On the other hand, carbon dioxide has been used to attract warble and throat bot flies, as well as blood-sucking insects for scientific purposes (Helle *et al.*, 1992; Anderson & Nilssen, 1996).

With the changing reindeer husbandry habits, defined chemical antiparasitics were adopted. In Russia, dichloro-diphenyl-trichloroethane (DDT) was sprayed together with hexachlorane against harassment by blood-sucking insects as well as warble and throat bot flies (Saval'ev, 1968). To treat a herd of 1000 reindeer, 12.5 kg of pure DDT and the same amount of hexachlorane was needed for one summer season. According to the author, carefully performed treatment increased the weight gain of the animals during the summer by 5 to 6 kg. The amount of warbles decreased also improving the quality of hides. Other insecticides were found effective as well; both chlorophos and pyrethrum (pyrethrin I) were found to act faster than DDT (Saval'ev, 1968).

If warbles become less abundant for example due to antiparasitic treatment, serological tests may be used in early detection of infected animals (see Monfray & Boulard, 1990).

Throat bot

Throat bots are also called nasal bots (Dieterich & Craigmill, 1990), nostril fly larvae (Helle, 1980), nose bot fly larvae (Nilssen & Haugerud, 1995) and nasal warble fly larvae (Saval'ev, 1968). Besides the scientific name *Cephenomyia trompe*, also an erratic form, *Cephenomyia trompe*, has been used (also in publications I-III). The confusion in the scientific name is based apparently on a 150 years old mistake (see Zumpt, 1965). After that, both names have been used, and the erroneous form *Cephenomyia* has been very common. Modeer (in 1786) is generally considered the author of the original description, but as Linné obviously knew the parasite already in 1722, some scientists have regarded him as the original author. The geographical distribution of throat bots follows rather closely that of warbles (Bennett & Sabrosky, 1962; Skjenneberg & Slagsvold, 1968).

Temporally, the life cycle of *C. trompe* resembles that of *H. tarandi*. The bots mature in tonsil pouches (Rehbinder & Nordkvist, 1983) during the spring, drop down to the ground, pupate and emerge as mature flies in the summer. The flies have mating places on prominent hill-tops. After mating, the female flies expel uterine fluid with larvae to the muzzle of reindeer (Anderson & Nilssen, 1990). The larvae invade the tonsil pouch, where the development is very slow in the beginning (Hadwen, 1926; Nilssen & Haugerud, 1995). Rapid development starts in the spring. Earlier, definitive diagnosis of throat bots required the slaughter of animals (e.g. Nilssen & Haugerud, 1995).

Before the commercial pharmaceuticals became available to reindeer herders, tobacco water was used for «deworming» throat bots. It was poured into the pharynx via the nostrils or mouth (Nieminen, 1989). Bots could also be removed manually by inserting a petroleum jelly lubricated hand into the mouth and pharynx of a well restrained animal. This task was entrusted to small-handed women or youths, and could only be carried out on adult reindeer (Saval'ev, 1968).

When throat bot flies were noticed to have specific mating places, attempts were made to kill the flies there by spraying the mating hilltops with hexachlorane (Saveljev, 1972). The method was never widely used, as main concern also in Russia was given to the treatment of parasitic stages with

organophosphates (Nepoklonov *et al.*, 1973). Later, it has been found that mating sites are far too numerous to be practical targets for control (Nilssen & Anderson, 1995a). The mating sites of *H. tarandi* are even more difficult to control in practice (Anderson *et al.*, 1994).

In the 1950's and 1960's, several systemically administered organophosphates were experimented with in Russia and some of them were found efficacious against reindeer warbles and throat bots (Savel'ev *et al.*, 1972; Nepoklonov *et al.*, 1973). Good efficacy of famphos, trichlorfon and fenthion against these parasites was reported also in Sweden (Nordkvist, 1967, 1980). In Finland, the organophosphates fenthion and famphur were taken into practice in the late 1970's (Mykkänen, 1978) and their good efficacy against warbles (Nieminen *et al.*, 1980) and throat bots made them popular in a short period until the ivermectin era began.

Arachnids

Arachnids can also give trouble to reindeer. Locally in Russia, reindeer are known to be parasitised by both sarcoptic and chorioptic mange mites (Saval'ev, 1968). *Sarcoptes scabiei* causes first small vesicles but later the affected skin may become covered by even a few centimetres thick scabs. Reindeer suffering from sarcoptic mange gradually lose their condition. During winter the weight loss is rapid, and the affected reindeer may perish (Saval'ev, 1968). The disease can be transmitted to humans, too. Once, the source of sarcoptic scabies in Taimyrian reindeer was traced to infected cattle (Mitskovich & Savel'ev, 1984).

Chorioptic mange mites cause local bald spots with no thick scabs and are not considered as serious pathogens as sarcoptic mange mites (Saval'ev, 1968). Rather apathogenic appearing chorioptic mites (*Chorioptes texanus*) are known from the ears of reindeer in Canada (Sweatman, 1958) and Finland (S. Nikander, unpublished). Apart from that, reindeer parasitic mites are not known from Fennoscandia.

As sarcoptic mange was considered an important reindeer health problem in Russia, means of chemotherapy were developed. In spring and summer hexachlorane and hexachlorane-creolin liniments were used, or if the situation was considered really serious the whole animals were dipped in solution containing the same medication. In winter, dipping of the reindeer would lead to chilling, so the animals were treated by fumigation. The reindeer was placed in an airtight chamber with a hole for the head. Inside the chamber, a cast iron stove was heated with timber. A tray filled with

sulphur was placed on the stove to produce sulphur dioxide fumes. The treatment lasted for 40-45 minutes and was repeated one week later. Also the reindeer harnesses, saddles and accessories were fumigated. An important part of mange control was also the isolation of infested animals and herds (Saval'ev, 1968).

Pentastomids

Reindeer are parasitised by one member of the phylum; *Linguatula arctica* is morphologically close to the widespread (although not prevalent) *L. serrata* of dogs and other species of tropical carnivores. *L. arctica* is called «sinus worm» because it lives in the paranasal sinuses of reindeer, especially calves. The species and different aspects of life cycle, epidemiology, pathogenity, taxonomy and antiparasitic treatment of *L. arctica* have been described and reviewed by Haugerud (e.g. 1986, 1989; Haugerud *et al.*, 1993).

No interspecific covariation

In one study, there was no association between the reindeer brainworm and gastrointestinal nematode infection intensities measured as faecal larva and egg counts (Karter, 1993). Likewise, no interspecific covariation was found in intensities of the brainworm, abomasal nematodes, warble, throat bot, and sinus worm in 351 reindeer calves examined *post mortem* from herds where antiparasitic treatment had not been performed (Nilssen *et al.*, 1998). So, a high (or low) warble burden is not indicative of the size of the abomasal nematode burden in the individual. The study also indicates transmission, not immunity, to be the key factor for parasitic infection.

MACROCYCLIC LACTONE ENDECTOCIDES

There are already thousands of publications on the macrocyclic lactone (ML) endectocides. This review is highly selective to include just those considered pertinent to the introduction to the subject of this thesis.

History of the endectocides commercially available

Ivermectin

The experience with many insecticides, anthelmintics and antibacterial antibiotics shows that revolutionary new drugs may soon lose their efficacy as evolution produces pests resistant to the new drugs. However, the discovery of the extremely high antiparasitic properties of a new group of macrocyclic lactones produced by soil

actinomycetes opened a totally new era in the antiparasitic treatment of livestock in the late 1970's and early 1980's. The group was called avermectins (*a* - negation, *ver* - worms, *ect* - ectoparasites, *in* - pharmaceutical product) (Shoop *et al.*, 1995). The producing actinomycete was thereafter named as *Streptomyces avermitilis*. The first commercial application, launched in 1981, a semisynthetic derivative of avermectin B₁, is called 22,23-dihydroavermectin B₁, or ivermectin. It is a mixture containing not less than 80% of the component B_{1a} and not more than 20% of the component B_{1b}, both of which molecules have antiparasitic activity (Shoop *et al.*, 1995). Because of the very high commercial success of ivermectin (Ivomec[®], MSD, now Merial), intense activity was triggered in the fields of chemistry, pharmacology and parasitology to find even more effective molecules, or at least commercially feasible ones.

Since the launch of ivermectin in 1981, until 1998, another five commercial ML endectocides have been introduced for use in production animals.

Abamectin

Abamectin, or avermectin B₁, was developed by the same medical company as ivermectin and is, interestingly, a natural fermentation product of *S. avermitilis*, and the direct raw material of ivermectin. Like ivermectin, also abamectin is a mixture containing not less than 80% of avermectin B_{1a} and not more than 20% of avermectin B_{1b}. Abamectin was registered in 1985 in Australia (Avomec[®], MSD) for the treatment of various endo- and ectoparasites in cattle and is now also available in Europe (Enzec[®], Janssen) (Heinze-Mutz *et al.*, 1993). The nematocidal and acaricidal activities of abamectin surpass its insecticidal activity (Shoop *et al.*, 1995). Abamectin is also used in crop protection (Dybas, 1989) which may be a cause of environmental concern as much as avermectin use in farm animals.

Moxidectin

The next endectocide to reach the market was a milbemycin derivative. The milbemycins (*milbe* - mite, *myc* - fungus, *in* - pharmaceutical product), like avermectins, are 16-membered macrocyclic lactones. They differ from the avermectins as they do not have the bisoleandroxyloxy substituent at the 13-position of the macrolide ring (McKellar, 1994). The milbemycins were already detected before the avermectins, but their full antiparasitic potential was not realised immediately. First they were aimed against mites in crop production (Shoop *et al.*, 1995). The actinomycete *Streptomyces cyaneo-*

griseus ssp. *noncyanogenus* produces a milbemycin called nemadectin (apparently *nema* - nematode, *ect* - ectoparasites; Zulalian *et al.*, 1994). Chemically modified nemadectin becomes moxidectin (the name from the *methoxime* substitution of the carbon C23). Moxidectin is marketed (Cydectin[®], American Cyanamid, now Fort Dodge) world-wide for domestic animal endectocide treatment.

Moxidectin is one hundred fold more lipophilic than ivermectin as measured by the standard octanol/water partitioning ratio. The lipophilicity of moxidectin causes that it is preferably stored in fat and this storage probably contributes to the much longer depletion half life measured in sheep than that of ivermectin (Hayes, 1994).

Moxidectin is more efficacious against nematodes in domestic ruminants than ivermectin, to the extent that ivermectin resistant nematodes may appear moxidectin sensitive (Pankavich *et al.*, 1992; Craig *et al.*, 1992; Pomroy & Whelan; 1993; Várady *et al.*, 1995) in spite of the probably similar mode of action and demonstrated cross-resistance (Shoop *et al.*, 1993; Le Jambre *et al.*, 1995). The long depletion half life causes that the persistent activity of moxidectin against nematode infections in domestic ruminants is longer (Taylor *et al.*, 1993; Hubert *et al.*, 1995). Injectable moxidectin at 200 µg/kg is reported to have high efficacy against cattle warbles (*Hypoderma lineatum*) (Scholl *et al.*, 1992), but there is also a report on poor efficacy of oral moxidectin at 400 µg/kg against third instar larvae of the equine bots *Gasterophilus* spp. (Xiao *et al.*, 1994). In one trial, injectable moxidectin had 96% efficacy against first instars of *Oestrus ovis*, but 100% against second and third instars (Puccini *et al.*, 1994). It appears that the anthelmintic properties of moxidectin are more pronounced than its insecticidal activity (Shoop *et al.*, 1995). Cattle dung has been less toxic against insects following moxidectin than following ivermectin treatment (Strong & Wall, 1994).

Doramectin

The fourth rival in the endectocide market is doramectin, 25-cyclohexyl-5-*O*-demethyl-25-de(1-methylpropyl) avermectin A_{1a}, produced by a mutant strain of *S. avermitilis*. The generic name obviously does not mean anything, but may give an impression of durability. In cattle doramectin has almost twice as long a half-life as 22,23-dihydroavermectin B_{1a}, the major component of ivermectin (Goudie *et al.*, 1993). Doramectin is marketed for sc injection (Dectomax[®], Pfizer) in sesame oil with ethyl oleate solution which contributes to low tissue irritability (Wicks *et al.*,

1993; Nowakowski *et al.*, 1995). Doramectin is claimed to have an antiparasitic spectrum close to that of abamectin (Shoop *et al.*, 1995).

Eprinomectin

The latest endectocide was presented in 1996-97. Eprinomectin (Shoop *et al.*, 1996) comes from the same pharmaceutical company as ivermectin and abamectin, although the company is now called Merial. The generic name eprinomectin is perhaps based on the chemical name 4''-epi-acetyl-amino-4''-deoxy-ivermectin B₁. To begin with, eprinomectin is only marketed as pour-on (Eprinex[®], Merial). Eprinomectin is a racemic mixture of compounds which comprises not less than 90% of the component B_{1a} and not more than 10% of the component B_{1b}. Probably the most obvious practical advantage of the product is its zero milk and meat withdrawal (in the USA). The commercial formulation contains 0.5% of eprinomectin, and the rest is fractionated oils of natural sources.

Mode of action

The mode of action of the different ML endectocides is similar at any rate in that it is not totally understood (McKellar & Benchaoui, 1996). Efficacy has been demonstrated against nematodes and arthropods, with some exceptions, such as the nematode *Thelazia lacrymalis* and the mite *Ornithonyssus sylviarum* (Campbell & Benz, 1984). Later, ivermectin has been found efficacious against other species of *Thelazia* (Kennedy *et al.*, 1994). The efficacy of ivermectin against equine cyathostome larvae is low (Klei *et al.*, 1993), but that of moxidectin is significantly higher (Xiao *et al.*, 1994). In one study, no efficacy of even high doses of ivermectin was seen against various nematodes in domestic fowl (Oksanen & Nikander, 1989). Avermectin activity was explained to be caused by binding to GABA-mediated synapses (Bennett, 1986). In vertebrates, there are GABA mediated synapses only within the central nervous system. Recent evidence shows that avermectins also interact to a nematode specific glutamate-gated chloride channel distinct from GABA-sensitive chloride channels, which is now considered the main mode of action (Turner & Schaeffer, 1989; Arena *et al.*, 1995). The chloride ion flux into neurones is the probable cause of the observed paralysis and death of the parasites. However, these may not be the only modes of action. Because of the closely similar chemical structure, antiparasitic spectrum and cross-resistance, it is likely that the mode of action of milbemycins is similar to that of

avermectins (Shoop *et al.*, 1995). In nematodes, low concentrations of ML endectocides have been shown to paralyse pharyngeal pumping, which leads to starving due to the worm's inability to feed. Higher concentrations inhibit motility, which might lead to a faster expulsion because the parasite loses its ability to swim against the tide of digesta (Gill & Lacey, 1998). The expulsion of *Ostertagia circumcincta* takes longer than that of *Haemonchus contortus* or *Trichostrongylus colubriformis* in sheep, which has been interpreted to suggest that the main method of expulsion in the first-mentioned species would be the inhibition of feeding, while the latter species probably are expelled due to inhibition of motility (Gill & Lacey, 1998).

Dosage and efficacy

The manufacturers' dose recommendations are based on dose titration trials with various parasite species. The susceptibility of different parasite species and their developmental stages vary a lot. The dose recommended is designed to be effective against the least susceptible target parasite species, in ruminants *Cooperia* or *Nematodirus* species. At the time of the introduction of ivermectin, 90% efficacy was considered very good and 80-90% moderately effective (Powers *et al.*, 1982). However, the endectocides themselves have changed the standards, currently a drug is regarded as highly effective if it has over 98% efficacy against the parasite species in question, effective if the efficacy is 90-98%, and moderately effective if 80-89% (Wood *et al.*, 1995). Against *Nematodirus helvetianus*, the efficacy of ML endectocides has been only moderate (Benz *et al.*, 1989), with the exception of moxidectin, which has high efficacy (Flochlay & Deroover, 1997). Before eprinomectin none of the drugs had established label claims against both adult and immature *Nematodirus* in cattle.

The recommended dose to domestic ruminants is the same 200 µg/kg for all the commercial endectocides for subcutaneous injection and oral administration, and 500 µg/kg for pour-on application. Eprinomectin is so far only marketed as a pour-on at 500 µg/kg for cattle.

For other animal species the dosage recommendations vary. The least dose widely used is that of oral ivermectin against canine heartworm microfilariae, given monthly at 6 µg/kg, while demodectic mange of dogs is treated with an oral dose of 600 µg/kg daily even for months (Ristic *et al.*, 1995). The latter is extra-label use, the manufacturer does not officially recommend

ivermectin at high doses for dogs and cats, at least partly because ivermectin can cause fatal intoxications in dogs, especially collies (Paul *et al.*, 1987). The standard dose in swine is 300 µg/kg against all ivermectin sensitive parasites (Sutherland, 1990).

In red deer (*Cervus elaphus*), the subcutaneously administered standard dose 200 µg/kg of ivermectin was found to give insufficient nematocidal efficacy, so the authors recommended doubling the dose (Andrews *et al.*, 1993). However, even the double dose 400 µg/kg did not give efficacy comparable with that of 200 µg/kg in cattle. The low efficacy was associated with pharmacokinetics; the peak concentration and AUC in red deer remained considerably lower than in cattle. It has been reported that pour-on eprinomectin at 500 µg/kg has high activity against strongyle parasites and lungworm in red deer (Gogolewski *et al.*, 1997).

Ivermectin has been observed to be extremely efficacious against cattle warbles, *Hypoderma lineatum*, close relatives of reindeer warbles. A high efficacy of injection was reported at a dose of 0.2 µg/kg - one thousandth of the recommended dose (Drummond, 1984). Ivermectin pour-on at 2 µg/kg has also been highly efficacious in the chemoprophylaxis of cattle warbles (*Hypoderma bovis* and *H. lineatum*) (Benakhla *et al.*, 1998).

Pharmacokinetics and route of application

Pharmacokinetics of ivermectin in domestic ruminants has been reviewed by Bennett (1986) and Steel (1993) and of various ML endectocides by McKellar & Benchaoui (1996). The ivermectin absorbed to the circulation is almost totally excreted in the bile. Because of lipophilicity of ivermectin, the volume of distribution is large, larger in sheep than in cattle (4.6 l/kg versus 1.9 l/kg) (Lo *et al.*, 1985). The larger distribution volume causes the plasma concentration to be intrinsically lower and the clearance rate more rapid in sheep than in cattle. The mean volume of distribution in cattle was also quite different for ivermectin (3.35 l/kg), doramectin (2.92 l/kg), and moxidectin (13.6 l/kg), respectively (Lanusse *et al.*, 1997). The large distribution volumes (especially that of moxidectin) are probably caused by distribution in adipose tissue. The distribution volumes vary a lot between different endectocides and animal species, thus affecting the plasma concentrations available for parasites.

A lot of commercial endectocide preparations have appeared to be used for different animal species, including man. For ruminants the main methods of application are subcutaneous injection,

oral liquid, pour-on (topical percutaneous), and ruminal sustained-release bolus. Common to all these application methods is that as an endectocide the drug is designed to act systematically, so it is essential that the active ingredient is absorbed to the blood circulation, in any case to get maximum activity against parenteral parasites.

In one trial, the area under the plasma concentration-time curve (AUC) was 5718 (s.e.m. 1203) ng*h/ml following subcutaneous injection of ivermectin at 200 µg/kg to sheep, and 2039 (231) ng*h/ml following oral administration at the same dose (Marriner *et al.*, 1987). The difference here was 2.8-fold. The AUC in goats after similar oral administration was only 516 (81) ng*h/ml (Scott *et al.*, 1990). Following sc injection to goats, the AUC of ivermectin was 1440 (144) ng*h/ml (Alvinerie *et al.*, 1993). The AUC for ivermectin, doramectin, and moxidectin in cattle following similar sc administrations of commercial preparations was 10790 (1128), 15048 (744), and 5208 (384) ng*h/ml (Lanusse *et al.*, 1997). In sheep, the AUC following sc dosing of moxidectin (2696 (499) ng*h/ml) was slightly higher than following oral dosing (2373 (375) ng*h/ml) (Alvinerie *et al.*, 1998). Based on earlier efficacy studies, the authors concluded that there was a relationship between plasma concentration and moxidectin efficacy.

Plasma concentration (Alvinerie *et al.*, 1998), and more specifically AUC, is perhaps the best explaining factor of the level of endectocidal efficacy of a given endectocide in a given animal species. This interpretation cannot, however, be expanded between different ML endectocides (Table 1) because of their different intrinsic antiparasitic efficacies. Neither is the efficacy against intestinal nematodes fully explainable with AUC as these parasites also may encounter the proportion of orally given drug that is not absorbed (McKellar *et al.*, 1991). On the other hand, ivermectin was not detected at all in abomasal fluid of sheep after sc injection at 200 or even 2000 µg/kg (Bogan & McKellar, 1988).

In the world endectocide literature there were 4436 papers listed until mid November 1998 in CAB abstracts only (CAB International, Wallingford, Oxon, UK). Most of them report excellent antiparasitic efficacy of one or more methods of endectocide application. Some papers also describe trials comparing the efficacy of two or more of the drugs. Relatively few, by contrast, compare the efficacy following various methods of application of the same drug in ruminants.

Table 1. Some plasma pharmacokinetic parameters of ML endectocides in different ruminants

Species	Drug	Dose (mg/kg)	n	Cmax (ng/ml)	tmax (h)	AUC (ng*h/ml)	Reference
Cattle	IVM	0.2 sc	5	54.6	35	10 790	Toutain <i>et al.</i> (1988)
Cattle	IVM	0.2 sc	4	42.8	96	11 016	Lanusse <i>et al.</i> (1997)
Cattle	IVM	0.2 sc	4	48.2	72		Herd <i>et al.</i> (1996)
Sheep	IVM	0.2 sc	5	30.8	60	5718	Marriner <i>et al.</i> (1987)
Goat	IVM	0.2 sc	5	6.12	68	1440	Alvinerie <i>et al.</i> (1993)
Red deer	IVM	0.2 sc	4	15.8	20		Mackintosh <i>et al.</i> (1985)
Red deer	IVM	0.2 sc	10	15.3	28		Andrews <i>et al.</i> (1993)
Red deer	IVM	0.4 sc	10	28.3	28		Andrews <i>et al.</i> (1993)
Sheep	IVM	0.2 po	5	22.0	16	2039	Marriner <i>et al.</i> (1987)
Goat	IVM	0.2 po	6	16.0	<24	516	Scott <i>et al.</i> (1990)
Cattle	IVM	0.5 topic	4	28.3	48		Herd <i>et al.</i> (1996)
Goat	IVM	0.5 topic	6	4.00	48	317	Scott <i>et al.</i> (1990)
Cattle	IVM	SR ^a	4	10.2	924		Herd <i>et al.</i> (1996)
Cattle	DRM	0.2 sc	20	27.8	72-144	11 400	Nowakowski <i>et al.</i> (1995)
Cattle	DRM	0.2 sc	4	37.5	144	15 048	Lanusse <i>et al.</i> (1997)
Cattle	MXD	0.2 sc	3	75.0	4-6		Miller <i>et al.</i> (1994)
Cattle	MXD	0.2 sc	4	39.4	7.7	5208	Lanusse <i>et al.</i> (1997)
Sheep	MXD	0.2 sc	5	8.3	21	2696	Alvinerie <i>et al.</i> (1998)
Sheep	MXD	0.2 po	5	28.1	5.3	2373	Alvinerie <i>et al.</i> (1998)

IVM ivermectin, DRM doramectin, MXD moxidectin

^aSustained release bolus, contains 1.72 g of ivermectin and is designed to release 12.7 mg daily for 135 days.

The small number of direct comparisons of different application methods in domestic ruminants (sheep) indicate a higher efficacy of subcutaneous compared with oral application (McKellar *et al.*, 1988a; Zajac *et al.*, 1992). Subcutaneously applied ivermectin had a persistent efficacy of at least 10 days against *Haemonchus contortus*, *Trichostrongylus vitrinus* and *Cooperia curticei*, but orally administered ivermectin showed no persistent efficacy (Borgsteede, 1993). A persistent efficacy lasting for one week was also seen for *Ostertagia circumcincta* (Grimshaw *et al.*, 1997). There is a 35 day persistent efficacy against *O. circumcincta* and *H. contortus* of both orally and subcutaneously administered moxidectin in sheep, and a high

persistent efficacy of sc administration against *Trichostrongylus colubriformis* 21 days after treatment but no efficacy 21 days after oral treatment (Kerbouef *et al.*, 1995). Persistent efficacy is well-known from cattle treated sc with endectocides (e.g. Barth 1983; Armour *et al.*, 1985; Vercruyse *et al.*, 1997; Meeus *et al.*, 1997; Ranjan *et al.*, 1997). In one trial, injectable moxidectin was rather effective against first instars of the ovine nasal bot *Oestrus ovis*, but oral drench was not (Dorchies *et al.*, 1996). Both the therapeutic and persistent efficacy of ivermectin injection against *O. ovis* were higher than those of oral ivermectin (Dorchies *et al.*, 1997). The greater efficacy of sc injected endectocides is related to pharmacokinetics; the bioavailability of ruminally

administered ivermectin was only 25%, whereas that of subcutaneously injected ivermectin was 100% (Prichard *et al.*, 1985). The initial explanation to the low utilisation of orally administered drug was that it was probably metabolised in the rumen, but later evidence indicates that ivermectin is bound to the particles of the digesta (Andrew & Halley, 1996). Anyhow, the low bioavailability remains a widely accepted fact.

In mountain sheep (*Ovis canadensis*), injectable ivermectin at 200 µg/kg offered an effective means of treating lungworm (*Protostrongylus* species) infection (Miller *et al.*, 1987), but orally administered ivermectin at approximately 400 µg/kg was ineffective (Easterly *et al.*, 1992).

There are also reports showing that oral application of ivermectin had superior anthelmintic efficacy when compared with subcutaneous injection. One was in goats and another in dromedary camels. In goats, the report describes a faecal egg count reduction test showing 94% efficacy of ivermectin injection at 200 µg/kg, compared with 100% efficacy for ivermectin oral formulation, obviously at the same dose rate. No details were given on the group sizes. It was discussed that *Trichostrongylus* spp. might have been the predominant nematodes in the goats (Pearson & Rutherford, 1988). In dromedary camels, trichostrongylid egg counts were reduced by 100% when ivermectin was administered orally and by > 88% when given subcutaneously, both at the dose of 200 µg/kg. Egg counts of *Trichuris* sp. were reduced by > 85% with oral administration, but increased following subcutaneous treatment (Boyce *et al.*, 1984). In both these cases the parasites in question appear to have been intestinal nematodes which may be affected also by the unabsorbed fraction of orally given ivermectin.

Topical pour-on administration of ivermectin to cattle at a dose of 500 µg/kg has been shown to cause high antiparasitic therapeutic and persistent activity (Alva-Valdes *et al.*, 1986; Yazwinski *et al.*, 1994; Williams & Broussard, 1995). Pharmacokinetic studies, however, show that the maximum plasma concentration and the AUC following such a treatment are smaller than those following subcutaneous administration despite the 2.5-fold dose (Herd *et al.*, 1996). In goats, subcutaneous ivermectin at 200 µg/kg lead to an AUC 4.5-fold that after topical administration at 500 µg/kg (Scott *et al.*, 1990; Alvinerie *et al.*, 1993).

Endectocide resistance

Parasite resistance refers to the recommended dose of drug now removing 95% or less of the resident parasite population (Hennessy, 1997). Resistance is now considered a major threat to parasite control world-wide (Waller, 1994, 1997). The first reports on ML endectocide resistance in nematodes emerged within 5 years after the introduction of ivermectin in 1981. Resistance has been observed mostly in *Ostertagia* and *Haemonchus* nematodes of small ruminants (Gill & Lacey, 1998). Endectocide resistance has been observed also in *Cooperia* species in a herd of cattle where oral ivermectin had been the only anthelmintic used in the strategic control programme over the previous two years (Vermunt *et al.*, 1995). Generally, factors contributing to anthelmintic resistance include frequent treatment and under-dosing, while alternating between different anthelmintic groups will slow down the establishment of resistance (Waller, 1990). So far, there are no reports on endectocide resistance in reindeer parasites; the low efficacy of ivermectin against the brainworm *E. rangiferi* is not a sign of resistance as ivermectin has never been regarded as effective against this parasite. After treatment of an animal with endectocides, declining drug levels over time will allow establishment of resistant infective larvae, while still eliminating susceptible larvae. To elucidate the population-level importance of these resistant larvae, computer simulations have been performed. The results from such simulations indicate that adult survivors of treatment have much greater importance than selection of infective larvae by decaying drug concentrations (Dobson *et al.*, 1996). The persistent efficacy of endectocides is favourable in preventing resistance, because more persistent drugs will remove resistant adult parasites more effectively. As anthelmintic resistance does not disappear spontaneously, it is important to try to prevent its initial establishment (Waller, 1990).

Also insects may become resistant to endectocides. In a trial with house flies resistance against abamectin developed rapidly and to a very high level (60 000-fold) (Scott *et al.*, 1991). So far there are obviously no reports on endectocide resistance in oestrid parasites, but there is no reason to believe that development of resistance would not be fully possible.

Gains of endectocidic treatment in domestic ruminants

Because of the high antiparasitic efficacy of the ML endectocides, it is not surprising that different

treatment programs have been observed to increase meat production (e.g. Suarez *et al.*, 1991; Baggott *et al.*, 1994; Williams *et al.*, 1995) or milk production (Ploeger *et al.*, 1989; Walsh *et al.*, 1995). In all of these five papers, pharmaceutical industry is represented, either as authors or acknowledged, which does not reduce the value of the individual papers, but indicates that animal health companies have interest in this kind of research. Therefore, publication bias appears possible, perhaps some studies with undesired results of treatment have remained unpublished.

Environmental aspects

The possible adverse effects ML endectocides might have to dung degradation fauna have raised much concern. After the first study (Wall & Strong, 1987), discussion has been lively. A number of studies have been performed on the degradation of cattle dung from ivermectin treated animals. Most scientists have found that degradation is retarded and insect fauna disturbed in dung following ivermectin treatment (e.g. Strong, 1993; Holter *et al.*, 1994). Researchers affiliated to Merial (former MSD) have stressed the importance of methodology when planning such studies (e.g. Barth, 1993). They showed that in addition to diptera and beetle larvae, treatment reduced the numbers of dung specific nematodes. However, they did not see retardation in dung degradation (Barth *et al.*, 1994). In a comparison of sustained release bolus, pour-on and subcutaneous injection ivermectin treatments, it was found that maximum concentration (2 days post treatment) in the faeces of pour-on treated animals was 12-fold higher than of the sc injected animals, but after one week the concentrations declined at a similar rate. The animals treated with a sustained release bolus, by contrast, produced faeces with a high ivermectin concentration till the end of the trial, 7 weeks post treatment. Both the sustained release bolus and pour-on treatments were considered more ecotoxic than the sc injection as judged by their higher faecal ivermectin concentrations (Herd *et al.*, 1996). This is not surprising, because the total treatment doses are higher. Oral ivermectin formulations were regarded as least ecotoxic due to the rapid excretion (Herd, 1995).

Apparently, no life cycle assessment (LCA) (e.g. Consoli *et al.*, 1993) of these compounds/drugs have been published, but obviously, the less the use, the less the production, and the less the environmental concern due to the manufacturing, and the less the risks of environmental damage due

for example to accidental leaks during production or delivery.

Ivermectin in reindeer

Because antiparasitic treatment of reindeer was a subject of common interest (Nieminen *et al.*, 1980; Reh binder *et al.*, 1981; Persen *et al.*, 1982) at the time of the introduction of ivermectin, it was natural that ivermectin given as a sc injection at the dose 200 µg/kg was immediately to be evaluated as an endectocidic antiparasitic to reindeer. In Sweden, a trial was done with 37 reindeer calves to compare the efficacy of four antiparasitics (ivermectin, fenthion, fenbendazole and mebendazole) against warbles, throat bots, brainworms, lungworms and abomasal and intestinal nematodes (Nordkvist *et al.*, 1983). Ivermectin was 100% efficient against warbles, throat bots, lungworms and abomasal and intestinal nematodes (*Nematodirus* species). The efficacy against brainworm larvae was lower. This is concomitant with results from white-tailed deer (Kocan, 1985). Fenthion had 100% efficacy against throat bots and 86% against warbles, but no efficacy against nematodes, while the benzimidazoles fenbendazole and mebendazole were 100% efficient against brainworm larvae and moderately-highly efficient against other nematodes. The benzimidazoles had no efficacy against warbles or throat bots. The high antiparasitic efficacy of ivermectin was confirmed in the next trial, performed in 1982-83 (Nordkvist *et al.*, 1984), which also showed a smaller weight loss during winter in ivermectin treated reindeer calves than in non-treated ones. To gain approval by the United States Food and Drug Administration (FDA) for ivermectin to be used in reindeer, a series of trials was performed in Alaska in 1982-83 (Dieterich & Craigmill, 1990). Ivermectin was considered safe to reindeer and efficient against warbles, and the tissue residues decreased rapidly, approaching zero by day 24. Based on these data, the FDA established a 56 day withholding period (double that of cattle). The next reported trial was initiated in 1984 in Norway. The live weight of reindeer calves about six months of age, treated with ivermectin during the autumn increased during the subsequent year on average 3 kg more than that of similar untreated animals (Heggstad *et al.*, 1986). In December, 1990, eighty reindeer calves were ivermectin treated in Kautokeino, Norway. In February, 14 of these treated and 19 control calves were slaughtered. The efficacy against throat bots was 100% and against the sinus worm, *Linguatula arctica*, 98% (Haugerud *et al.*, 1993).

The arctic and subarctic dung degradation fauna can be expected to be less tolerable than that of more temperate regions. The concern on the possible negative effects of ivermectin treatment has been discussed in Norwegian newspapers (e.g. Berg 1991). Recently, a method was developed to analyse ivermectin residues in reindeer faeces (Åsbakk *et al.*, 1999), and one trial was done to investigate the degradation fauna of reindeer faeces after sc ivermectin injection (Nilssen *et al.*, submitted). Although measurable concentrations could be shown in faeces produced for 30 days post treatment, the impact on dung insect fauna was

negligible, because the winter faeces from lichen-fed animals did not attract insects during the next summer regardless of ivermectin treatment, obviously due to its nutrient-poor and dry structure.

The difference in antiparasitic activity of the various endectocides and their various formulations in domestic ruminants makes it necessary to compare the activity in reindeer, where high efficacy against insect parasites is required. Because of the inhibited development of hypobiotic nematode parasite larvae during the time of treatment (Nordkvist *et al.*, 1984), there are also special nematocidal efficacy requirements.

Aims of the research

The aims of the present study were:

1. To find ways to optimise the current endectocidal antiparasitic treatment methods of reindeer, taking into account the efficacy of the treatment and economical as well as ecological considerations. The goal was thus to look for the best drug and the best way of administration as well as the ideal timing.
2. To develop research methods needed to fulfil the aim #1.
3. To investigate, whether summer treatment against subclinical infections of calves to be slaughtered in the autumn might be economically feasible.

Materials and methods

Study design

Most of the trials described in these publications were designed for aim #1 (Table 2). Trial I compared the antiparasitic efficacy of oral (as the equine paste formula) and subcutaneous administration of ivermectin against nematodes and warbles. Work III added pour-on ivermectin, and efficacy was also measured against throat bots, according to the method described in paper II (aim #2). Paper IV used chemical analyses to explain the differences in antiparasitic efficacy discovered in trials I and III. Trial V was designed to evaluate a new drug, moxidectin, as a reindeer endectocide. Publication VI described the insecticidal efficacy (against warbles and throat bots) of doramectin in reindeer. Paper VII compared the antiparasitic efficacy of oral ivermectin given at different times

Table 2. Experimental animals and their endectocide treatments.

Paper	Untreated group	IVM inj. 200 µg/kg	IVM oral 200 µg/kg	IVM topical 500 µg/kg	Other treatment	Year
I	A ^a 31 (28) ^b	A 31	A 30 (29)			1989-90
II	C 8					1991
III	A 13	A 13 (12)	A 13	A 13	A 13 (10) ^d	1990-91
IV		C 5	C 5	C 4, A 6, C 5		1991, 1993
V	A 14 (13)	A 14			A 14 (13) ^e	1991-92
VI	A 20 (19)				A 20 ^f	1994-95
VII	A 18 (16)		A 54 (51) ^g			1995-96
VIII	C 177 (75) (8) ^c	C 177 (59) (9)		C 175 (62) (9)		1995

^a A=adults, C=calves

^b the number in parenthesis is the final sample size after exclusion of missing animals.

^c counted alive (breeding replacements).

^d IVM injection 20 µg/kg, ^e MXD injection 200 µg/kg, ^f DRM injection 200 µg/kg, ^g oral IVM 200 µg/kg, either in September, December, or February.

IVM ivermectin, DRM doramectin, MXD moxidectin.

during the autumn or winter.

Papers I, III, V, VI and VII include development of methodology to evaluate efficacy against hypobiotic nematode parasites (aim #2).

One trial (VIII) was performed exclusively for aim #3.

Animals and experimental design

Most of the experiments (I to VII) were done in the Kaamanen Experimental Reindeer Herd of the Finnish Association of Reindeer Herding Co-operatives in Kaamanen, Inari (69°09'N, 27°00'E) during the winters 1989-1990 to 1995-1996. Most trials used naturally infected adult hinds (females) (I, III, V, VI, VII), but in two trials, also males were included (I, VI). If animals were to be slaughtered, yearlings were used (II). If frequent blood sampling was required (III), reindeer calves about 8 months old were used, in addition to Norwegian adult reindeer and Swedish yearlings (see below). All experimental animals were individually marked, either with numbered collars or ear tags, or both. It is a routine in Kaamanen to gather the herd monthly for weighing and occasional blood sampling. There are slightly over 100 hinds in the herd, the number of calves varies a lot between years. The area for the herd is about 43 km² of pine and birch forests and fells (Nieminen, 1998).

The hinds were allocated to the groups using stratified randomisation according to age (I, III, V, VII), or just randomly by lot (VI). The calves were allocated according to sex and weight (IV). The group size varied between 10 (III) and 31 (I). Paper (IV) described three trials; A, five yearlings from Könkämä, Sweden; B, six adult reindeer from Dielddasuolo (Tjeldøy), Norway; and C, three groups of five calves each in Kaamanen.

Endectocide treatment

The endectocidal treatments were performed in December (I, III, V, VI), in November, January or May (IV), in September, December or February (VII), or in July (VIII). The drugs used were ivermectin, Ivomec[®] 10 mg/ml vet inj., MSD (Merial) (I, III, IV, V, VIII), Ivomec[®] vet 18.7 mg/g pasta (=Eqvalan[®] paste), MSD (I, III), Ivomec[®] vet mixt. 0.8 mg/ml, MSD (VII), Ivomec[®] pour-on for cattle, MSD (III, IV, VIII), moxidectin, Cydectin[®] 1% vet inj., American Cyanamid (Fort Dodge) (V), or doramectin, Dectomax[®] 1% vet inj., Pfizer (VI). Subcutaneous injections were given in front of the left shoulder (lateral midline of the neck) at a dose of 200 µg/kg (I, III, IV, V, VI, VIII) or similarly at a dose of 20 µg/kg (III). Oral administration was given over the base of tongue at a dose of 200

µg/kg (I, III, IV, VII). Topical pour-on treatment was given under the hair coating over the back between the shoulder blades ("spot-on") at a dose of 500 µg/kg (III, IV), or as a narrow strip along the back from withers to the base of tail at the same dose rate (IV, VIII). The untreated controls were given no placebo (I, III, V, VII, VIII) or were given physiological saline at 1 ml/50 kg sc (VI).

To investigate the possibilities of endectocides used as «growth promoters» in reindeer calves, 529 calves from two herding co-operatives (Palojärvi and Kemin-Sompio) in Finnish Lapland were allocated systematically to three groups during ear-marking in July, 1995. One group was left untreated, the other was injected subcutaneously with ivermectin at 200 µg/kg and the third received pour-on ivermectin topically at 500 µg/kg. Carcass weights of animals slaughtered during the autumn or winter were then compared between treatment groups (VIII).

Examination for adverse reactions

Because both the standard injection and oral applications of ivermectin had been used in reindeer husbandry and also experimented with in the Kaamanen herd (Soveri *et al.*, 1990), no specific follow-up for adverse reactions was undertaken in the first trial (I), but the animals were observed in connection with other animal management tasks. In trial (III) with the new topical ivermectin treatment, the animals were released after treatment into an outdoor enclosure where they were observed at times for 24 hours. A similar follow-up for adverse reactions, but of different durations, was undertaken following moxidectin and doramectin treatments (V, VI). Were animals found dead due to unknown cause during the experiments, they were autopsied, if possible.

Faecal examination for nematode eggs or larvae

To facilitate the evaluation of nematocidal efficacy, faecal egg counts (FEC) were done. The nematode eggs were identified to the genus *Capillaria* if they were rough-shelled, about 50 µm in length, dark-stained, of barrel shape and with slightly protruding polar plugs, to the genus *Skrjabinema* if they were typical to the genus: about 50 to 70 µm long, thin-shelled and markedly asymmetrical (rather like an orange section), or as trichostrongylids if they were indistinguishable from those of the family Trichostrongylidae: oval or ellipsoid, not markedly asymmetrical, thin-shelled and length 60 to 100 µm. As the trichostrongylid egg counts were expected frequently to be negative due to hypobiosis at the time of treatment in midwinter,

faecal examination was performed several times during winter and spring. The FECs were done with modified McMaster technique using saturated NaCl solution with sucrose (Christensson *et al.*, 1991), each egg observed representing 40 egg (I, III) or 20 egg (V, VII). The individual monthly trichostrongylid FECs were used to calculate Faecal Egg Count Mean (FECM) (V, VII). Microphotographs of parasite egg specimens are presented in Appendix 2.

Brainworm and lungworm larvae were examined according to a Baermann technique (Holmström *et al.*, 1989) (I, III). Larvae were identified as those of the brainworm, *Elaphostrongylus rangiferi*, if they were of the proper size (0.3 to 0.4 mm) and had one cuticle and the characteristic dorsal spine over the tail. Similar sized larvae with one cuticle, but without the dorsal spine over the tail were classified as those of the lungworm, *Dictyocaulus* sp. (*Dictyocaulus eckerti*).

Warble and throat bot examination

Warbles were counted as described earlier (Nordkvist, 1967; Dieterich & Craigmill, 1990). In late March - early May, when the larvae had reached the 3rd instar stage, but before a considerable amount of them had left the host (Nilssen & Haugerud, 1994), the backs of the experimental reindeer were examined visually and by digital palpation (I, III, V, VI, VII). If the number of warbles exceeded 30, the count was done in tens as adjacent warbles might blend together and prevent exact enumeration.

Warbles from the calves slaughtered in January were counted by visual examination of the inside of the skin (VIII).

The endoscopy method for counting throat bots (II) was used in late April or early May (III, V, VI, VII).

Animal weighing

The Kaamanen reindeer were weighed using an ovine balance modified to enable the weighing of reindeer (Poldenvale lambway, Precision Weighers, Reading, England, 1 kg reading intervals) (I, III, IV, V, VI, VII). The new-born calves were weighed within 24 hrs of birth (spring balance, 100 g intervals) (III, V, VII). Other than Kaamanen animals were weighed using available apparatus. The calves in paper VIII were in the trial start weighed on a standard bathroom balance (1 kg reading intervals), and their carcass weights were taken from the slaughter records.

Chemical analysis

To help explain the difference in antiparasitic efficacy, plasma concentrations were measured from reindeer calves treated with ivermectin administered in different ways (IV). The analyses were performed by Merck Research Laboratories, Lauterbach, Germany, using a HPLC (high pressure liquid chromatographic) method with fluorescence detection (Downing, 1989).

Statistical analysis

Faecal egg counts (FECMs) and animal weights were compared by one-way analysis of variance. If the group effects were statistically significant ($P < 0.05$), Tukey test was used for pairwise comparison of the group means. In paper VIII, Student's *t* test, χ^2 test, Mann-Whitney test, and one-way analysis of covariance were performed. The number of warbles and throat bots differed so much between treatment groups (treatment efficacy often 100%) that it was usually not tested at all. However, in one trial (VI) the proportion of animals infested with warbles and throat bots was compared by χ^2 test. In paper VIII, Mann-Whitney test was used to compare the number of warbles. To compare the weights of calves born to hinds treated with untreated controls during the different years, Kruskal-Wallis one way analysis of variance was used. The statistical analyses were carried out using the Statgraphics® 2.6 program package or the Statistix® software package, either version 3.5, 4.0, or 4.1. One-way analysis of covariance was done with BMDP software.

Results

Adverse reactions

No adverse reactions were noticed following any of the ML endectocidic treatments administered in any of the various ways of application. The single autopsied animal showed no signs of tissue irritation at injection sites. The death was not associated with endectocide treatment.

Efficacy against nematodes

No effect of ivermectin or moxidectin treatment could be seen against the sporadic *Skrjabinema* egg production (V). The eggs were found only in April and May, 4 to 5 months post treatment. The question remains if the treatment however had had efficacy, and the egg production was caused by reinfection. In study I, both oral and injected ivermectin reduced the *Capillaria* egg production. In trial III, this post-treatment reduction could be

seen in all the groups, including the untreated control group. In trial V, both moxidectin and ivermectin appeared to reduce the *Capillaria* egg production, but the difference in the egg counts was not significant. In trial VII, *Capillaria* eggs were detected so infrequently, and in so small numbers, that they were totally omitted from the paper.

There was a statistically non-significant reduction of lungworm larva production in animals treated with ivermectin. The reduction was more pronounced following injection than oral administration (I). In study III, the lungworm larva output followed the same pattern as in trial I: the larvae were absent from the samples of February, and the mean value remained low (it only equalled or exceeded 1 lpg in the orally treated and control groups in May). The difference between the treatment groups was not statistically significant, but the average larva production was lowest in the standard (200 µg/kg) injection group. The number of brainworm larvae in faeces (I, III) was so low and their excretion so sporadic that no calculations on treatment efficacy were justified, but efficacy was definitively not very high.

Trichostrongylid FEC was reduced by both the sc and oral treatments in trial I. Egg output was first observed in the untreated control group, and followed in successive intervals by the orally treated group and the injection group. The FEC was significantly lower in the injection group than in the untreated group in March and June, and in the injection group than in the oral group in April. No Faecal Egg Count Means (FECM) for individual animals were calculated in this trial.

Similar reduction in trichostrongylid egg output was seen in the next study (III). Egg production of the standard injection group was first observed in April, a month later than in the other groups. The FECMs of the standard injection group were significantly lower than those of the other groups. The standard sc injection reduced the FECM by 80%, both oral treatment and 20 µg/kg injection by 39%, and the topical pour-on application by 35%.

Injectable moxidectin and ivermectin reduced the trichostrongylid FECM by 92% and 95%, respectively (V).

In trial VII, oral ivermectin (Ivomec® vet mixt. 0.8 mg/ml, MSD) reduced the trichostrongylid FECM by 62 to 74%.

Efficacy against warbles and throat bots

All ivermectin treatments in autumn/winter at 200 or 500 µg/kg were 100% effective against warbles and throat bots (I, III, V, VII). Injectable ivermectin at 20 µg/kg had also 100% efficacy against warbles,

the efficacy against throat bots was 92% (III, data not fully shown). Injectable doramectin at 200 µg/kg had 100% efficacy against both warbles and throat bots (VI). Moxidectin at 200 µg/kg had 93% efficacy against warbles and 71% against throat bots (V).

The persistent (prophylactic) efficacy of injected (200 µg/kg) or pour-on (500 µg/kg) ivermectin reduced the number of warbles in hides of reindeer calves treated in midsummer by about 60%.

Pharmacokinetics

Plasma concentrations were constantly higher in reindeer calves given ivermectin as sc injection than in those that received it either orally or as pour-on (IV). The mean maximum concentration following standard sc treatment was about 5-fold that of the orally treated animals. The concentration also decreased more slowly following sc treatment; after 7 days the difference in concentrations was 14-fold between the injection and oral groups. The mean maximum concentration after topical treatment varied much between the three trials, the highest one was in the animals treated in May (about one third of that of the standard sc treatment in January). The lowest mean maximum concentration was in the animals treated in January (about one twenty-fifth of that of the standard sc treatment). No AUC was calculated due to the small number of sampling times, but it was clearly much larger following sc injection than other treatments, despite the higher dose given topically.

Weight development

In the first trial (I), the (mostly pen-fed) animals gained weight during the winter, the untreated group 4.8 (s.e.m. 1.1) kg, compared with 5.5 (1.3) and 8.8 (1.5) kg, respectively, for the orally and injection treated hinds. The difference was not significant in ordinary one-way analysis of variance, but using the treatment as a continuous variable (0, untreated control; 1, oral treatment; 2, sc injection) the effect of treatment became significant. In the next study (III), weight loss was observed in all the groups between the time of treatment and early April, with no significant differences between the groups. In the trial with moxidectin and ivermectin injection (V), the mean weight gain between December and April was highest in the untreated group, 1.8 (1.5) kg compared to 1.0 (0.8) and 0.8 (1.3) for moxidectin and ivermectin treated animals, respectively. The difference between the groups was not significant.

Table 3. Mean birth weights (s.e.m.) of reindeer calves born to differently treated Kaamanen hinds.

Study nr.	Birth year	Untreated control	IVM inj. 200 µg/kg December	Other treatment
III	1991	5.14 (0.32)	5.51 (0.23)	5.53 (0.17) ^a
				5.45 (0.30) ^b
				5.55 (0.25) ^c
V	1992	5.24 (0.21)	5.63 (0.29)	5.55 (0.25) ^d
VI	1995	5.79 (0.25)		5.47 (0.28) ^e
VII	1996	5.69 (0.26)		6.22 (0.26) ^f
				6.65 (0.22) ^b
				6.42 (0.29) ^g

^a IVM injection 20 µg/kg December, ^b IVM oral 200 µg/kg December.

^c IVM topical 500 µg/kg December, ^d MXD injection 200 µg/kg December.

^e DRM injection 200 µg/kg December, ^f IVM oral 200 µg/kg September.

^g IVM oral 200 µg/kg February.

If two extreme weight gain/loss values were omitted as outliers, the weight gain of the control group was 0.5 (0.9) kg, compared to 1.0 (0.8) and 1.7 (1.0) kg for moxidectin and ivermectin treated animals. In hinds treated orally (Ivomec® vet mixt. 0.8 mg/ml, MSD) at different times (VII), the mean weight gain/loss of the groups of hinds varied between a loss of 2.6 kg and a gain of 1.6 kg, the untreated controls lost 0.1 kg.

No difference was seen in slaughter weights between reindeer calves treated with ivermectin during the summer and those untreated (VIII).

Birth weights

The mean weight of calves born to treated animals was often higher than that of untreated controls (Table 3). However, the differences between treatment groups were not statistically significant.

Discussion

The necessity to study endectocides in reindeer

The differences reported in endectocide efficacy, and especially pharmacokinetics (Table 1), between various animal species makes it impossible to reliably extrapolate efficacy and pharmacokinetics expectations from other ruminants. The closest relative to reindeer to which pharmacokinetics data was available is the red deer. In this species, the C_{max} was low, about 15 ng/ml, as compared with about 44 ng/ml in reindeer (trial IV). In red deer the

C_{max} was reached about 1 day after subcutaneous injection at 200 µg/kg, but in reindeer about 3 days after similar treatment. The low plasma concentrations in red deer were also associated with insufficient antiparasitic efficacy (Andrews *et al.*, 1993).

Study methods

In the current studies, the treatment efficacy determination against warbles and throat bots was based on direct parasite counts, which is the most reliable basis of efficacy calculation, and thus the method to be recommended (Wood *et al.*, 1995). These experiments (III, V, VI, VII) have apparently been the first utilisation of the endoscopic method for detecting throat bots in live reindeer (II). The inspection requires special equipment (human fiberoptic bronchoscope), but, apart from that, is quick, simple and relatively easy to perform. The examination takes generally less than one minute per animal, and most often the animals do not react to the insertion of the bronchoscope.

Because of limited funding, animals could not be slaughtered, so it was essential to be able to use FEC as an indirect measure of nematode parasite burden. As the treatments were performed during winter when nematodes are hypobiotic and start to produce eggs only months later, the common practice of performing FEC reduction test 1-3 weeks post treatment (e.g. Coles *et al.*, 1992) could not be applied. The spring FECM used in the

current trials has the drawback that reinfection cannot be excluded as a source of parasite burden in any individual animal, or even a group of animals. However, if the comparison of FECMs can show difference between treatment groups, given that the groups are otherwise similar, this difference has to be caused by differences in treatment efficacy. Reinfection can only diminish the differences, and the reductions in FECM may be smaller than the actual antiparasitic efficacy. Therefore the differences observed tend to be conservative estimates.

The McMaster technique (Christensson *et al.*, 1991) as it was used in the first trials (I, III) had a sensitivity (40 epg) that was later considered suboptimal because of the rather low FECs common in reindeer during the winter and spring. Therefore the technique was modified so that each egg observed represented 20 epg. The change increased the laboratory work needed, but it increased even more the value of the examination. Together with the calculation of FECM based on several samples, probably a fair measure of the gastro-intestinal nematode burden was achieved.

Endectocide treatment of reindeer is different from domesticated ruminants

The treatment of reindeer with ML endectocides is different from their most common use in domestic ruminants as the treatment is directed against both insect and nematode parasites. In domestic ruminants endectocides are mostly used against nematode parasites, in fact they are often referred to as «anthelmintics» in this context. The other use of endectocides is as an insecticide in herd level or larger control programs, e.g. against lice or bovine warbles. Seldom can the broad spectrum of the compounds be utilised as thoroughly as in the yearly strategic antiparasitic treatment of reindeer.

Endectocidic efficacy of different ways of application

Antiparasitic treatment of reindeer with ML endectocides is a sequel to the organophosphate treatment against warbles and throat bots started in Finland in the 1970's. Killing warbles and throat bots with the current ML endectocides is easy; from the treatment protocols tried, only moxidectin at 200 µg/kg did not kill all warbles. The low dose of ivermectin at 20 µg/kg killed all warbles, but did not have complete efficacy against throat bots.

The endectocide doses used in the current trials are those used in other ruminant species, too. The sc ivermectin injection at 200 µg/kg is also officially registered for use in reindeer in Finland.

The sc injection at 20 µg/kg in trial III was chosen to be a dose clearly smaller than the registered one.

The broad spectrum of ML endectocides gives reindeer owners, and especially reindeer veterinarians, a new responsibility when compared to insecticide treatments. As the endectocides have high efficacy against various nematode parasites, the treatment creates a selection pressure on the nematode fauna. Some of the reindeer nematodes, like those from other cervids, may also be shared with domestic ruminants (Nilsson, 1971; Borgsteede, 1982; Bye & Halvorsen, 1983). Frequent use of the drugs increases the risk of the rise of resistant nematode strains. Even though reindeer treatment cannot currently be considered frequent, it is important to minimise also other factors that might favour endectocide resistance. One of the best-known of them is underdosage (Waller, 1990), i.e. treatment that does have lower killing efficacy than expected. Obviously, the higher the efficacy, the better.

In reindeer, probably only intestinal nematodes, such as *Nematodirus*, *Nematodirella*, *Capillaria*, and *Skrjabinema*, may be significantly affected by the unabsorbed fraction of orally administered ML endectocide. The importance of these parasites to reindeer health is unknown. Abomasal nematodes living in close connection to abomasal mucosa probably are very little influenced by the drug concentration in the bypassing digesta. To ensure maximal efficacy of ivermectin treatment against warbles, throat bots, sinus worms, lungworms, abomasal nematodes, brainworms and other nematodes, such as *Setaria*, *Onchocerca* and *Lappinema*, the drug should be given so that maximal AUC is achieved, as standard sc injection.

It is known that ivermectin treatment decreases the fertility of surviving (resistant) nematode females (McKellar *et al.*, 1988b; Le Jambre *et al.*, 1995). Because no animals were killed following treatment in the current studies, actual worm counts could not be performed. It is therefore not known whether the trichostrongylid gastrointestinal nematodes were killed after ivermectin (or moxidectin) injection or not. However, the time lag between the treatment and the first recording of egg production was so long (≥ 3 months) that a reversible reduction in fecundity would perhaps already have receded. The prepatent period, time from infection to the start of egg production, of various *Ostertagia* spp. is about three weeks (Soulsby, 1982), so, reinfection might well explain the trichostrongylid egg production in April-May. In any case, the efficacy of sc ivermectin injection has been unmistakably superior to that of the other

administration methods. The difference in FECs clearly indicates that oral and topical ivermectin did not have desired nematocidal efficacy. Orally applied ivermectin is mostly adsorbed to ingesta, and goes therefore into dung. Topically applied ivermectin is very uncertainly absorbed, which may be associated with the thick haircoat and hollow hairs (Timisjärvi *et al.*, 1984).

Unfortunately, market economics strongly affect the pricing of different ivermectin preparations. For example in Norway, where both injection, oral paste, oral mixture and pour-on preparations are available, a treatment dose (200 µg/kg as injection or given orally and 500 µg/kg as pour-on) to a 50 kg reindeer calf will cost NOK 8.11 (≈EUR 0.94) as sc injection, NOK 12.10 as equine paste, NOK 8.59 as pour-on, and only NOK 3.72 as oral mixture (Galligani *et al.*, 1996). The latter price is obviously so much lower to enable it to compete with benzimidazoles as an ovine anthelmintic. The active ingredient is cheapest as pour-on, to compensate for the higher dosage; pour-on at 200 µg/kg would cost NOK 3.44 for the same 50 kg animal.

Parasite adaptation to the Arctic

Although trichostrongylid eggs cannot be positively identified to species or even genus, in reindeer faeces they are mostly *Ostertagia gruehneri* (Bye, 1987; Fruetel & Lankester, 1989). The reindeer trichostrongylids appear to be well-adapted to the arctic climate by hypobiosis; the development is sustained so that egg production is ceased in mid-winter, which obviously saves both the parasites and the host. The parasite does not waste energy in reproduction when the eggs would be deposited on snow, where their chances of development might be small. The host, in turn, would be unnecessarily stressed by parasite activity in midwinter when food is scarce. It appears that the reindeer *Capillaria* parasites do not follow the same pattern, but produce eggs in mid-winter. Later, however, the egg production might decrease, while that of trichostrongylids increases. The *Capillaria* pattern is not as clear as that of trichostrongylids, and the factors behind are unknown.

Eradication?

In many countries, eradication programs have been established against cattle warbles (*H. bovis* and *H. lineatum*). These programs are based on the common conclusion that warbles harm the cattle industry enough to justify the costs of the campaigns (e.g. Tarry *et al.*, 1992). It is common to both reindeer warbles and throat bots that the total

overwintering population is in the reindeer host. If it was possible to once treat all reindeer, total eradication of these parasites would be just a matter of antiparasitic efficacy of the treatment, which is very high for subcutaneously administered ivermectin. However, all the reindeer are virtually impossible to find during any winter. Moreover, the wild reindeer populations could still serve as a reservoir. Even though the reindeer husbandry locally could agree that getting rid of these nuisances would be a common benefit, such agreement would probably not be accepted in all the reindeer herding areas. The adult flies when attacking reindeer are said to help to collect the animals in flocks (e.g. Nilssen & Haugerud, 1994), which is needed for the ear-marking in the summer. Some reindeer herders refuse to believe that the flies would be totally unnecessary and only harmful for reindeer. People who have lived long with the animals may understand that the evolution of the symbiosis between the reindeer and its parasites to the current stage has taken a long time; the parasites are part of the natural biodiversity and should therefore not be eradicated.

Economic feasibility

Only one of these studies (VIII) was designed to measure economic benefit of endectocidic treatment to reindeer, and that trial investigated summer treatment of calves, which is not currently practised in reindeer husbandry. In that trial, no increase in slaughter weights could be demonstrated. Because of the rather big sample size, it appears very unlikely that the result would have been caused by error alone. All the winter treatment trials were done in the Kaamanen herd, which might differ from commercial co-operative herds in terms of nutrition and parasitism. However, it is interesting to note that significant differences in weight development between treatment groups were only seen in one trial (I), and even then not in ordinary analysis of variance. The differences in calf birth weights between groups in trials III, V, VI and VII were not significant, either. This does not prove wrong the view expressed by many reindeer owners that ivermectin treatment enhances the condition of reindeer and helps the animals to survive over winter and produce healthy offspring. However, the lack of significant weight gain effects of endectocide treatment indicates that such effects might be dependent on other factors, such as crowding and nutrition. Such management differences may at least partly be the cause of the difference in results in weight gain studies of reindeer calves following summer antiparasitic

treatment. Unlike in trial VIII, in the two trials reported from Kaamanen, summer antiparasitic treatment increased the weight gain. Both of those trials were done with a relatively small amount of animals, so the results may be erroneous. However, it appears logical to think that year- and husbandry-related differences in parasite burden may have been the major source of difference in results. This should get practising veterinarians cautious in advocating treatment. Both the existing scientific results and the costs of treatment should be considered. Perhaps in some cases a good alternative to treatment would be not to treat. After all, reindeer meat is, and is expected to be, a natural product, and chemical antiparasitics do not fit well into this image. Ivermectin residues were found in the liver of one reindeer of 35 randomly selected for control by the Finnish National Veterinary and Food Research Institute in 1997 (Aalto *et al.*, 1998).

Timing

It seems that the current «treat them when you catch them» timing of the endectocide treatment is fully adequate. Parasites can be effectively treated anytime during the winter although nematodes are hypobiotic and oestrid fly larvae develop slowly. Similar antiparasitic efficacy and small and non-significant differences in weight gain/loss and in birth weights between groups treated either in September, December, or February (trial VII) indicate that the timing of endectocide treatment of reindeer is not critical.

Future research

Future research challenges are many. The low insecticidal efficacy of moxidectin in reindeer requires an explanation. Was it caused purely by the lower intrinsic efficacy of moxidectin against insects, or did the drug perhaps not reach the parasites? To clarify this, pharmacokinetics of moxidectin in reindeer should be studied. Those studies might also help to understand other differences, perhaps still unnoticed. For example it is not known how the nutritional status of animals, reindeer or other, affects the pharmacokinetics and antiparasitic efficacy of ML endectocides.

Pharmacokinetics of ivermectin in reindeer also need to be worked on further. The results from trial

VII might indicate that the active ingredient of the oral ivermectin mixture could be better bioavailable than that of the equine ivermectin paste. That possible difference might be caused by the mixture bypassing the rumen, as it has been shown that the bioavailability of abomasally applied ivermectin is far higher than that of ruminally applied. If such bypass exists, it should obviously be utilised thoroughly when ivermectin is administered orally to ruminants, as is now common in sheep industry.

To assess the relative economic importance of various reindeer parasite groups, narrow-spectrum antiparasitics should also be experimented with. Benzimidazole compounds do not have insecticidal efficacy, so they could be used as anthelmintics, while some insecticides, such as fenthion do not have anthelmintic efficacy.

If the nematocidal efficacy of doramectin eventually proves to be equal to that of ivermectin, doramectin is a good alternative in reindeer endectocidal treatment. Based on the knowledge from other animal species, this would not seem unlikely. However, it would be wrong to assume efficacy based on other animal species, so the nematocidal efficacy has to be tested.

Some of the currently commercially available ML endectocides have not been tested in reindeer at all. Abamectin is obviously a better nematocide than insecticide, which might be a benefit in reindeer treatment. The interest in under-dosage would be reduced, if its consequences were seen as warbled animals. However, for abamectin to be useful its insecticidal efficacy should be higher than that of moxidectin. If eprinomectin (as pour-on) is absorbed through the reindeer skin as it is designed to do through the bovine skin, it might be a good endectocide to reindeer. The general concern of wasting the active ingredient applies also to reindeer, but not necessarily more than to cattle. Perhaps eprinomectin also will be marketed as an injection sometimes, and possibly there will be other ML endectocides marketed in the future, too. All of them will apparently have similar mode of action, and therefore also cross-resistance will exist if it first has been established. To minimise the risk of endectocide resistance alternative antiparasitic methods should be investigated.

Conclusions

Subcutaneous administration

To direct the endectocide against important parasites, maximal bioavailability of the drug is needed. Having the standard sc injection as reference treatment, oral dosing (at least as the equine paste) of ivermectin can only be regarded as underdosing. To get comparable endectocidic efficacy, the oral dose should probably be at least 3- or 4-fold, which would not be ecologically nor economically feasible. Therefore, oral administration of ivermectin (perhaps all ML endectocides) to reindeer is principally to be condemned.

The results from these experiments, together with those from many trials in domestic ruminants, raise concern regarding the oral application of ML endectocides to ruminants, a common practice in sheep husbandry. Is this treatment really directed against relevant parasites? The most important ovine parasites are obviously nematodes of the abomasum, and it is in this group that endectocide resistance has been observed. Perhaps the treatments should be directed more specifically against these parasites. Then, the use of oral administration should be reconsidered in earnest.

Possible economic benefits of treatment still poorly known

The results from the summer ivermectin treatment of reindeer calves show that it is erroneous to expect gains based on trials with domestic animals. The economic feasibility of antiparasitic treatment of reindeer is poorly documented and not well-known. These experiments did not clarify the matter.

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Appendixes

Appendix 1. Names of some important nematode and arthropod reindeer parasites in some languages.

Latin	English	Norwegian	Swedish	Finnish	Saami
<i>Ostertagia gruehneri</i>	medium stomach worm	løpe-rundmark	löpmagsmask	juoksutus-mahamato	civzzamáhtu
<i>Dictyocaulus eckerti</i> ^a	lungworm	lungemark	lungmask	keuhkomato	geahpesmähtu
<i>Elaphostrongylus rangiferi</i>	brainworm	hjernemark	hjärnmask	aivomato	liw'zamáhtu
<i>Hypoderma tarandi</i> ^b	warble, grub fly	hudbrens	hudbroms, renstyng	kurmu, kurmupaarma	gurbmä-loddi, lávzá
<i>Cephenomyia trompe</i> ^c	throat bot, nasal bot	svelgbrens, nesebrens	svalgkorm, nässvalgstyng	saulakka, saulalintu,	njunne-loddi, sávla
<i>Solenopotes tarandi</i>	sucking louse	blodlus	blodlus	täi	varradihkki
<i>Damalinia tarandi</i>	biting louse	pelslus	pälslus	väive	náhkediikki
<i>Linguatula arctica</i> ^d	sinus worm	bihulemark, nese-flyndre	näshälemask	kielimato	njunnemáhtu, njunneguovdni

(Bergman, 1916; Nordkvist, 1966; Skjenneberg & Slagsvold, 1968; Nilssen & Anderson, 1986; Folstad, 1986; Hemmingsen, 1986; Haugerud & Nilssen, 1986; Paliskuntain yhdistys, 1992; J. Kitti, pers., comm. 1998, English names from the text).

^a Formerly regarded as *D. viviparus*, the bovine lungworm.

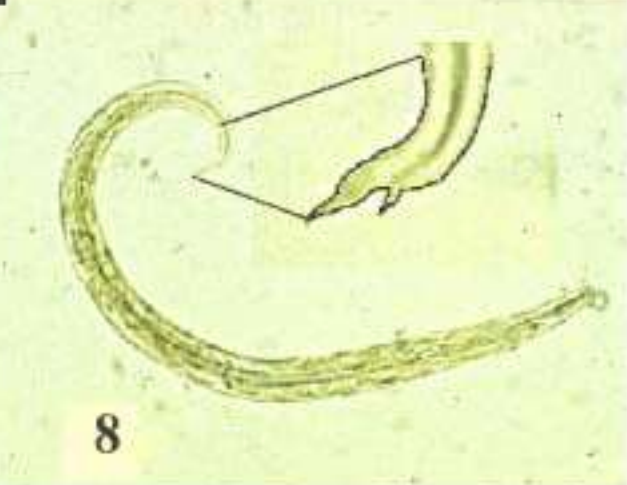
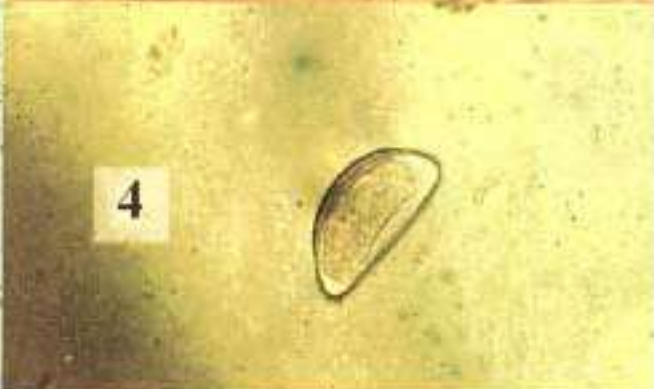
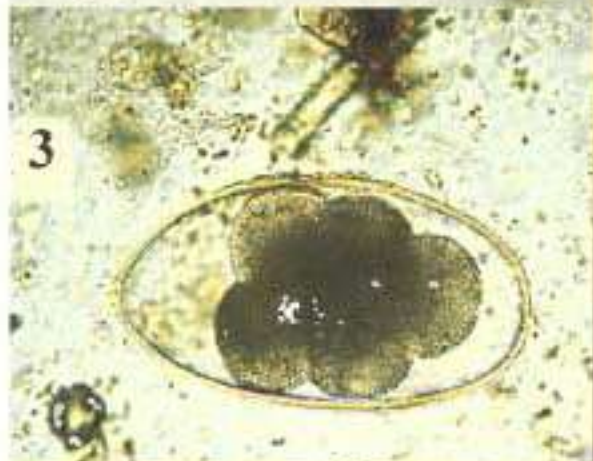
^b Formerly called *Oedemagena tarandi*.

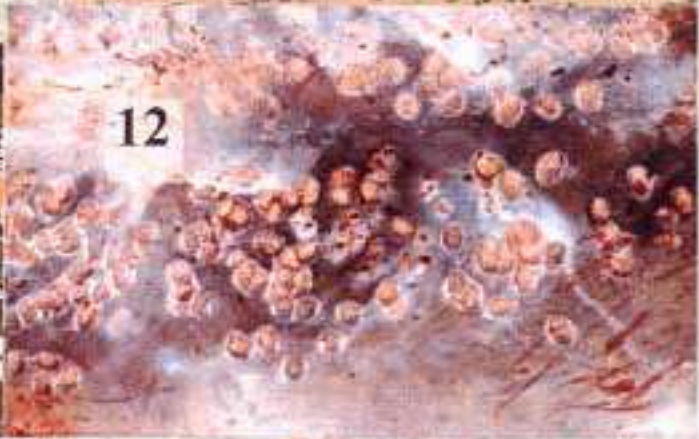
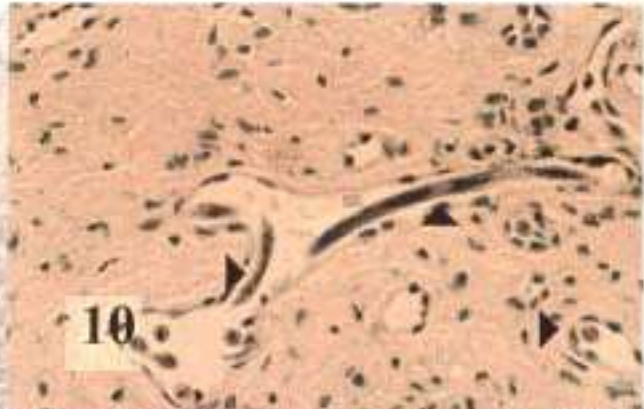
^c Often used the erroneous form *Cephenomyia trompe*.

^d Often in older literature erroneously called *L. serrata*, the canine sinus worm.

Appendix 2. Photomicrographs of parasite eggs and larvae in reindeer faeces and photographs of other reindeer parasites (diagnostic aids).

- 1-2. Gastro-intestinal trichostrongylid.
3. *Nematodirus* sp. Seen almost exclusively in reindeer calf faeces.
4. *Skrjabinema* sp.
5. *Capillaria* sp., together with *Eimeria* sp. coccidia oocysts.
6. *Moniezia* sp. (Cestode). Seen almost exclusively in reindeer calf faeces.
7. *Linguatula arctica* (Pentastomid).
8. *Elaphostrongylus rangiferi* I₁, dorsal spine not easily visible in print, therefore enlarged. Scale bar 100 µm for Figures 1-8.
9. Fibrous tissue caused by *Lappnema auris* in the auriculum of reindeer («wart-ear» or «hot ear»).
10. Histological section of fibrous tissue caused by *Lappnema auris*. Numerous parasites in capillaries (arrows). H-E staining.
11. Warbled reindeer hind in early May. The barren female has lost its antlers.
12. Warbled reindeer hide slaughtered in May. Inside view.
13. Cross-section of the skin of a reindeer calf, died in March, partly due to heavy warble infection.
14. Massive throat bot infection (101 bots) in a reindeer calf killed in May.
15. Throat bots seen in reindeer by fiberoptic pharyngoscopy.
16. *Linguatula arctica* from a reindeer calf slaughtered in May. Scale bar 8.5 cm.





Oral and parenteral administration of ivermectin to reindeer

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ABSTRACT

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The anti-parasitic effect of the orally administered paste formulation of ivermectin (Ivomec[®]) in reindeer was evaluated by means of a trial designed to compare the efficacies of orally and s.c. administered ivermectin at the same dosage (0.2 mg kg⁻¹ body weight) in naturally infected adult reindeer ($n=92$). Both formulations were 100% effective against larvae of the warble fly, *Oedemagena tarandi*, while oral treatment was less efficacious than s.c. injection against parasitic nematodes. Both formulations, but particularly the injectable ivermectin treatment, increased the weight gain of pregnant females compared to that of those not treated.

INTRODUCTION

The character of reindeer husbandry in Finland has changed considerably during recent decades. Demand for intensive production has replaced nomadic herding customs entirely with stationary reindeer farms and the traditional, more natural rearing systems with use of parasiticides and additional feeding in winter.

Before ivermectin, parasiticides were aimed against larvae of the warble fly (*Oedemagena tarandi*) and throat bot fly (*Cephenomyia trompe*). Organophosphates were used regularly and extensively in the late 1970s and early 1980s (Mykkänen, 1978; Nieminen et al., 1980), but the real breakthrough in the anti-parasitic therapy of reindeer was the introduction of ivermectin in 1982. During the last few years, about two-thirds of the total overwintering reindeer population have been treated with ivermectin (Nieminen, 1984, 1989). One routine treatment a year, in early winter, is considered sufficient

to control susceptible parasites. The flies are active only during the summer and reinfection by nematode larvae after successful treatment is considered unlikely until summer because the reindeer graze on separate summer and winter pastures.

Ivermectin, given *s.c.* at a dosage of 0.2 mg kg^{-1} body weight (b.w.), has been documented to be highly efficacious against most nematodes in cattle, sheep and other domesticated ruminants (Benz et al., 1989). Registration trials led Dieterich and Craigmill (1990) to conclude that the same dosage of ivermectin is safe for reindeer and efficient against warble fly larvae. Nordkvist et al. (1983) considered ivermectin to be the drug of choice against warble fly and throat bot fly larvae, lungworms and gastrointestinal nematodes in reindeer, in preference to fenbendazole, mebendazole and fenthion.

Ivermectin has been available in a paste formulation for oral (*p.o.*) administration to horses for years and the oral paste or liquid formulation is now available for sheep, goats and cattle in many countries (Di Netta, 1989). During the last few years, some Finnish reindeer owner associations have advocated the treatment of reindeer with the equine paste formulation and a preliminary trial by Soveri et al. (1990) demonstrated excellent efficacy against warble fly larvae, although the effect of the paste was less than that of the injectable compound against gastrointestinal nematodes.

The aim of the present work was to compare the efficacies of the orally administered paste formulation of ivermectin and the injectable product against warble fly larvae and nematodes parasitizing reindeer.

MATERIALS AND METHODS

The trial was carried out with naturally infected reindeer at the Kaamanen Reindeer Research Station in northern Lapland, an area characterized by bare fells and thin pine and birch forests.

A random allocation of the overwintering adults of the research herd (78 females and 14 males) was performed on 15 December 1989, dividing the animals into three groups: C, P and I. Treatments were given on the same date. Group C acted as untreated controls, Group P received ivermectin (Ivomec vet 18.7 mg g^{-1} pasta, MSD B.V., Haarlem, Netherlands) over the tongue at a dose of 0.2 mg kg^{-1} and Group I was treated with injectable ivermectin (Ivomec 10 mg ml^{-1} vet inj., MSD B.V., Haarlem, Netherlands) *s.c.* in front of the left shoulder at the same dosage. Five females from each group were free-ranging animals, while the rest was pen fed with lichen and commercial fodder in spacious enclosures ($8\text{--}10$ animals ha^{-1}).

Faecal samples were collected from the rectum just before treatment and 3, 6, 11, 15, 19 and 26 weeks later. A modified McMaster technique was used to detect helminth eggs and, when the sample size permitted, also a modified Baermann technique to observe lungworm and brainworm larvae. The

McMaster technique had a detection level of 40 eggs per gram (epg) and the Baermann technique (modified after Holmström et al., 1989) from 0.2 to 0.5 larvae per gram (lpg), depending on the amount of faeces available for the examination. The Baermann apparatuses consisted of 30 cc injection syringes (B-D Plastipak) with 0.15 mm sieves installed near the conical end under the faecal sample, filled with tap water and left standing overnight with the conical ends down. By pressing the piston, five droplets were forced out of each syringe onto a microscope slide for examination at $\times 40$ magnification.

The nematode eggs were identified to genus (*Capillaria* sp., *Nematodirus* sp. (possibly *Nematodirella*)), or as 'trichostrongyles'. Larvae were regarded as those of the brainworm, *Elaphostrongylus rangiferi*, if they were of the correct size (0.3–0.4 mm) and had one cuticle and the characteristic dorsal spine over the tail. Similar sized larvae with one cuticle, but without the dorsal spine over the tail, were classified as representing the lungworm, *Dictyocaulus* sp.

Warble fly larvae were detected and counted from each individual reindeer by visual examination and palpation on 27 March.

The animals were weighed monthly until 26 April, when the calving season was beginning.

Statistical analyses were carried out using the Statgraphics 2.6 program package (Statistical Graphics Corporation, 1986) for microcomputers. If the group effects were found to be statistically significant ($P < 0.05$) in one-way analyses of variance, the Tukey test was used for pair-wise comparison of the group means. Fisher's exact test was used to compare the prevalence of warble fly larvae between the treated and control animals.

RESULTS

On 15 December *Capillaria* eggs were discharged in moderate numbers in all three groups. Neither trichostrongyle eggs nor lungworm larvae were observed initially, and brainworm larvae only in minimal numbers (Figs. 1–4). A small number of *Nematodirus* eggs were seen in one sample.

The effect of the treatments was evident in the trichostrongyle egg and lungworm larva outputs. Egg and larva output was first observed in the control group (C) and followed in successive intervals in the paste group (P) and injection group (I) (Figs. 1 and 3). Statistically significant differences in trichostrongyle egg output were observed between Groups C and I on 28 March (15 weeks post-treatment) and 13 June (26 weeks), and between Groups P and I on 26 April (19 weeks). Statistical significance was not seen in the difference in lungworm larva output. *Capillaria* egg output was constantly higher in the control group, while the epg values for the two treated groups oscillated at a low level (Fig. 2). Group C differed significantly from both the others on 8 January (3 weeks) and 1 March (11 weeks), and from Group I also on 30 January (6 weeks). The difference narrowed on 28 March (15 weeks) and

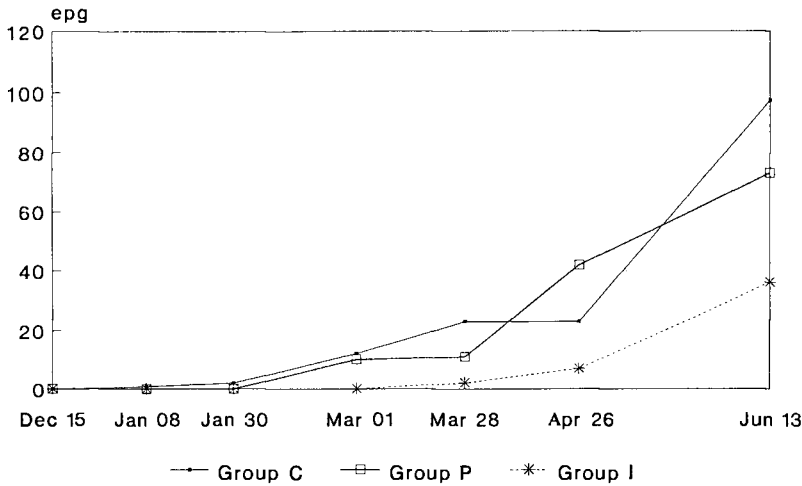


Fig. 1. Mean trichostrongyle egg output.

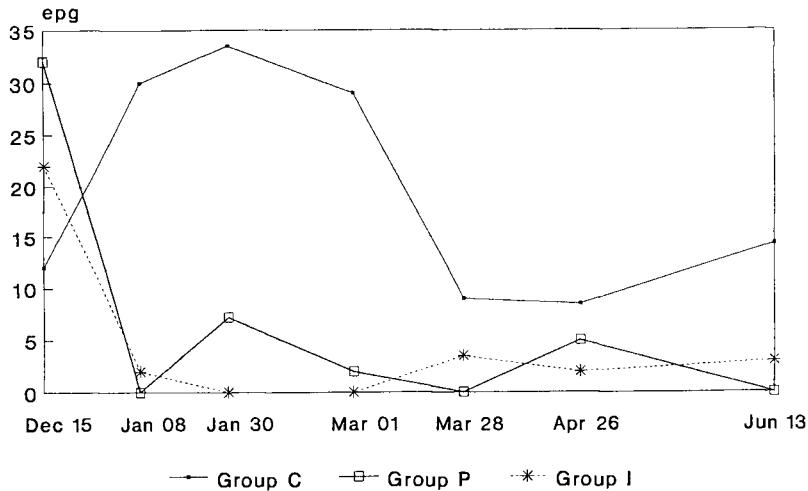


Fig. 2. Mean *Capillaria* egg output.

later because the egg output in the control group stabilized. The output of brainworm larvae remained low in the treated groups, but increased in the control group in January and March (Fig. 4). A peak value for controls was observed in April, but statistical significance was not observed.

On 27 March, the control group was found to harbour a moderate number of warble fly larvae, 41.6 ± 9.4 (mean \pm standard error of the mean (SEM)), while both the treated groups were totally free of these; the differences were significant.

The weight gain of the untreated females during the period 14 December–

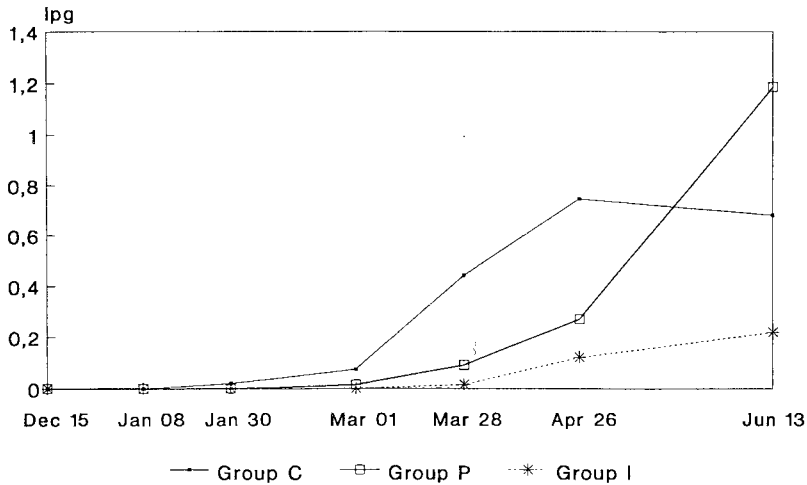


Fig. 3. Mean lungworm larva output.

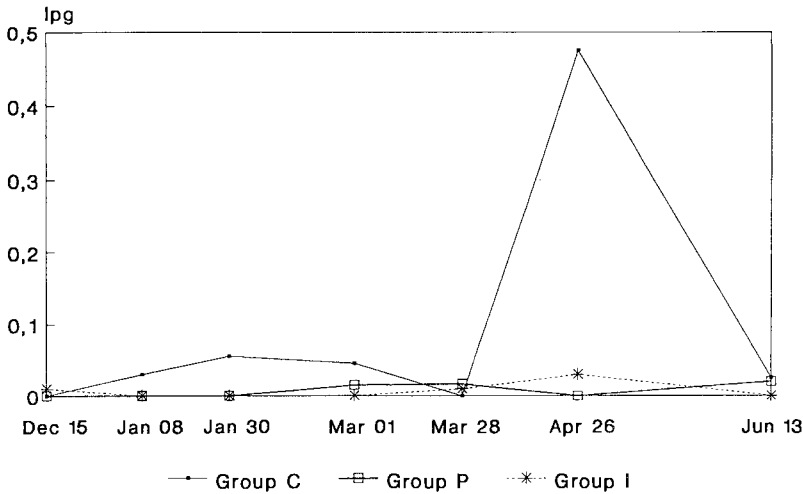


Fig. 4. Mean brainworm larva output.

26 April was 4.8 ± 1.1 kg (mean \pm SEM) compared with 5.5 ± 1.3 kg and 8.8 ± 1.5 kg, respectively, for Group P and I females. If Treatments C, P and I were coded as 0, 1 and 2, respectively, and were used as a continuous variable to explain the weight gain, the regression was statistically significant. However, the treatment effect was not great enough to be evident in an ordinary analysis of variance.

DISCUSSION

As could be expected on the basis of earlier research (Soveri et al., 1990), the effect of both ivermectin formulations was excellent against warble fly

larvae. Treatment also clearly increased the weight gain of the pregnant females when adequate food intake for all the groups was assured by means of pen feeding.

The increased output of trichostrongyle eggs and lungworm larvae in the control group as the spring proceeded indicated that these nematodes have adapted to the subarctic climate. Seasonally inhibited development of fourth stage larvae and young adults of trichostrongyles and lungworms has been confirmed in cattle and sheep (Soulsby, 1982), and has also been observed in nematodes of reindeer by Nordkvist et al. (1983, 1984), but Rehbinder and von Szokolay (1978) did not find inhibited larvae in the abomasa of winter-slaughtered reindeer. Inhibited development could benefit parasitic nematodes during the 6-month-long subarctic winter. The efficacy of both ivermectin formulations has been confirmed against inhibited abomasal nematodes in domestic ruminants (Benz et al., 1989).

The 1 month difference in the onset of trichostrongyle egg release between the present two treated groups is probably due to the higher efficacy of the injection treatment leading to a decreased parasite burden, which caused a delay in the spring rise of egg output. Another possible explanation is that the injection treatment caused further inhibition of already inhibited nematodes. The findings of Nordkvist et al. (1984) could be explained by the same mechanism. After ivermectin administration in late November, they found no reduction in the number of abomasal nematodes in necropsy examination in late April, although the living nematodes did not produce eggs as they did in the control group. The difference between the effects of the two administrations in the present trial may be due to either a higher tissue concentration of the drug when administered s.c. or a more persistent anthelmintic activity.

The observations by Nordkvist et al. (1983) of the low efficiency of ivermectin against the brainworm, *E. rangiferi*, gains additional support from the present results. Similar results from a trial with related host and parasite species were hypothesized to be due to the parasites being behind the blood-brain barrier, which ivermectin does not readily cross (Kocan, 1985).

The present experiment confirms the preliminary conclusions of Soveri et al. (1990). Although the ivermectin paste formulation effectively eliminated warble fly larvae, the anthelmintic efficacy of the paste was less than that of injectable ivermectin at the same dose. Thus, s.c. administration remains the recommended route of administration because of its overall efficacy and the possible reduction of the risk of development of resistant nematode strains.

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Fibreoptic pharyngoscopy for diagnosing throat bots in the reindeer

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Reindeer throat bots, *Cephenomyia trompe* (Diptera: Oestridae) larvae, are considered parasites of major importance, and, together with those of the warble fly, *Oedemagena tarandi*, main indications for antiparasitic treatment (1). According to Skjenneberg and Slagsvold (2), oedema in the pharynx caused by bots may spread to the meninges and brain and cause nervous symptoms, and mature bots may accidentally enter the trachea and even cause fatal bronchopneumonia. Reh binder (3) found 1st instar larvae in the affected eyes of about 25% of 90 reindeer suffering from keratitis. While warble fly larvae are easy to detect and the effectiveness of antiparasitic treatment is thus easy to evaluate, throat bots have proved difficult to confirm in live animals, and the assessment of the effect of treatment against them has been based only on autopsies. Thus, throat bots have just been excluded from some evaluations of the effects of antiparasitics on reindeer (4,5), while other authors have performed autopsies (1,6). Basic research into throat bots on reindeer and other cervids has

similarly been based on autopsies (7,8,9,10) with no possibilities for monitoring the development of the bots in individual host animals.

In order to detect bots in the nasopharynx of living reindeer, a fibreoptic bronchoscope designed for use with human patients (Olympus BF type B2) was tested on 60 one-year-old reindeer calves and 85 hinds on May 11th and 12th, 1991. The animals were restrained on a bench, with one man holding the head straight. The bronchoscope was slowly inserted into the left nostril medioventrally. In four of the 145 animals, the nostril had to be changed to manoeuvre the bronchoscope into the correct place or to get a better view. Less than ten animals coughed during or immediately after pharyngoscopy. No bleeding was observed in any of the animals. The examinations were performed without prior checking of the animals' antiparasitic treatment earlier in December. All but one of the 49 non-treated animals (98%) were found to harbour throat bots; a mean of 23 individuals (S.D. 11) being counted on 27

calves and 21 (12) on 22 hinds, whereas all the treated animals (given ivermectin as a subcutaneous injection, oral paste or percutaneous pour-on) were found to be free of bots.

Eight bot-positive calves were slaughtered immediately after laryngoscopy, and the larvae were collected from these, counted, weighed and their developmental stage determined according to the criteria given by Bennett and Sabrosky (8).

Endoscopy revealed 20 (S.D. 8) bots in the calves, while they were found upon autopsy to be harbouring 57 (48) bots. The proportion of 2nd instar larvae was 35%, the rest being 3rd instars. Endoscopy showed every animal to be positive, but never revealed

more than 30 bots, even though the reindeer harboured up to 136 individuals, 99 in this maximum case being 3rd instars (Table 1). It seems that at this time of the year, when the majority of the bots are 3rd instars, the maximum number detectable is about 20-30, the others being situated deeper in the pouch of the tonsil (*Tonsilla pharyngis dorso-medialis*) described by Reh binder and Nordkvist (9).

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Figure 1. Throat bots in the pharynx of a reindeer observed with fibre-optic pharyngoscopy.

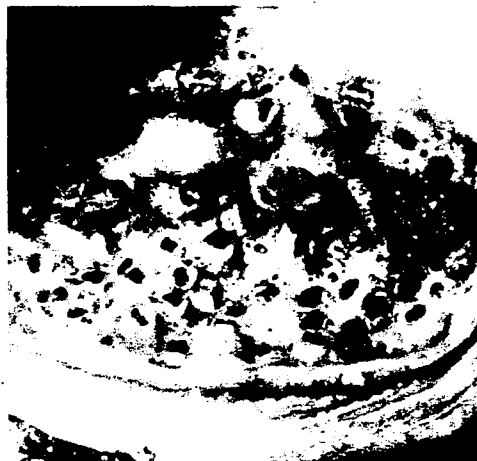


Figure 2. Throat bots in the pharynx of a reindeer calf at autopsy.

Table 1. Throat bots in reindeer calves examined May 11th-12th, 1991

Calf number	sex	bots found by endoscopy	bots found at autopsy	bot length min (mm)	bot length max (mm)	2. instars
4383	m	30	55	8	26	11
4388	m	30	136	6	29	37
4389	m	15	18	19	25	0
4396	f	5	7	8	14	7
7974	f	20	20	6,5	27	4
7994	m	20	95	6	30	27
7996	m	20	101	6	24	42
7999	f	20	23	13	23	1
average		20	56,9	9,1	24,8	16,1

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A comparison of topical, subcutaneous and oral administrations of ivermectin to reindeer

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The topical administration of ivermectin to adult reindeer hinds was evaluated by comparing its antiparasitic efficacy at a dose of 500 µg/kg bodyweight with that of oral administration at a dose of 200 µg/kg and subcutaneous administration at dosages of 20 and 200 µg/kg. The comparison included faecal examinations for nematode eggs and larvae and the counting of warbles and throat bots (*Oedemagena tarandi* and *Cephenomyia trompe* larvae). Weight changes and calf birth weights were recorded. All the treatments were 100 per cent effective against warbles and all except the low subcutaneous dose (20 µg/kg) against throat bots. The anti-nematodal efficacy of the topically applied ivermectin, the orally administered drug and the low subcutaneous dose was inferior to that of the subcutaneous dose of 200 µg/kg. There were no differences in weight changes between the groups.

PARASITISM is generally regarded as one of the most important causes of disease and poor condition in reindeer (Skjenneberg and Slagsvold 1968). Ivermectin has proved to have an unsurpassed antiparasitic spectrum and activity compared with other parasitocides (Nordkvist and others 1983) and is now widely accepted for routine use in Finnish reindeer husbandry. The standard regimen is to give animals in the breeding stock one subcutaneous injection at a dose of 200 µg/kg bodyweight when the flock is rounded up in early winter for the selection of those to be slaughtered. Oral administration at the same dose has also been used on

a smaller scale, employing a paste product registered for use with horses in Finland. This product was shown in a recent trial to be highly effective against warbles (*Oedemagena tarandi* larvae), but its efficacy against gastrointestinal nematodes was inferior to that of the standard subcutaneous injection (Oksanen and others 1992a).

The topical pour-on preparation (Ivomec pour-on for cattle; Merck & Co/Merck Frosst) is not registered in Finland but is available for use with cattle in many other countries, including Sweden. Reports of trials with cattle (Alva-Valdes and others 1986, Taylor and others 1990) and red deer (Mackintosh and others 1990) indicate good antiparasitic efficacy at a dose of 500 µg/kg. Topical administration of ivermectin to reindeer has not previously been reported.

The efficacy of topical application to reindeer was evaluated by comparing its antiparasitic efficacy in adult hinds at a dose of 500 µg/kg with that of oral administration at 200 µg/kg and subcutaneous administration at 20 and 200 µg/kg.

Materials and methods

Adult, naturally infected reindeer hinds of the Kaamanen research herd in northern Lapland were randomly allocated into five groups on December 11, 1990: group C, controls, remained untreated, group D, decimal dose, were treated subcutaneously with ivermectin in front of the left shoulder at a dose of 20 µg/kg and group I, standard dose were treated similarly at a dose of 200 µg/kg (Ivomec 10 mg/ml; MSD BV); group O, oral, received 200 µg/kg over the tongue (Equalan paste; MSD BV) and group T, topical, were treated topically with 500 µg/kg (Ivomec pour-on for cattle; Merck & Co/Merck Frosst Canada) using a 10 cc injection syringe connected to a 5 cm long flexible tube to apply the material under the hair on the back between the shoulder blades. All the treatments were given in a shed at a temperature of about 10°C, and the animals were immediately released into an outdoor enclosure where they could be observed for adverse reactions for 24

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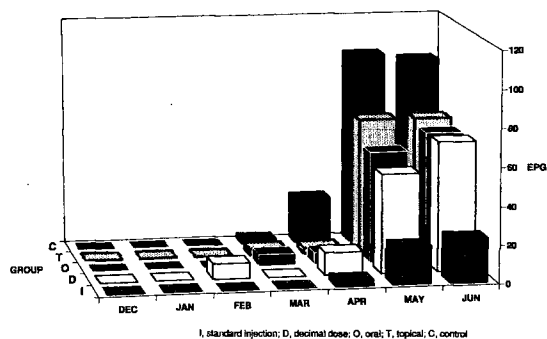


FIG 1: Mean trichostrongyle egg output in the treatment groups

hours. The weather outside was dry and frosty (-10°C). Throughout the trial the animals were free-ranging in a fenced fell and forest area of about 1400 hectares. They were rounded up monthly until June for the taking of individual faecal samples from the rectum on December 11, January 7, February 13, March 8, April 8, May 11 and June 11. As it was not possible to find all the hinds every time, it was decided to exclude from the experiment any of the animals missing from the faecal sampling more than twice. As a result the numbers of animals in the experimental groups were group C 13, group D 10, group I 12, group O 13, and group T 13.

The faecal samples were analysed by a modified McMaster method to detect nematode eggs, and also by a modified Baermann method (Oksanen and others 1992a) when the sample was large enough, to detect brainworm and lungworm larvae. The modified McMaster method had a detection level of 40 eggs/g (epg) and the Baermann method 0.5 to 0.2 larvae/g (lpg), depending on the amount of faeces available for examination.

The nematode eggs were identified as belonging to the genus *Capillaria* if they were rough-shelled, dark-stained, of barrel shape and with slightly protruding polar plugs, or as 'trichostrongyles' if they were indistinguishable from those of the family Trichostrongylidae: oval or ellipsoid, not markedly asymmetrical, thin-shelled and of length 60 to 100 µm. Larvae were regarded as those of the brainworm, *Elaphostrongylus rangiferi*, if they were of the appropriate size (0.3 to 0.4 mm) and had one cuticle and the characteristic dorsal spin over the tail. Similar-sized larvae with one cuticle but without the dorsal spine over the tail were classified as representing the lungworm *Dictyocaulus* species.

Warbles were counted visually and by digital palpation on May 11 and 12 and throat bots (*Cephenomyia trompe* larvae) were counted at the same time by using a human fibre-optic bronchoscope according to the method described by Oksanen and others (1992b). When collecting the faecal samples, the animals were weighed on a sheep balance modified for reindeer (Poldenvale lambway; Precision Weighers) marked at 1 kg intervals. The newborn calves were weighed within 24 hours of birth on a spring balance marked at 100 g intervals.

Differences in outputs of parasite eggs and larvae were assessed by calculating individual means over the period from January to June and converting the data logarithmically (epg=log(epg+1)). The converted values were compared by one-way analyses of

variance and if a significant difference was found, the Tukey test was used to assess the difference more accurately. The numbers of warbles and throat bots were compared in the same way. Weight losses were compared by using an ordinary one-way analysis of variance. The statistical analyses were performed using Statistix 3.5 software (Anon 1991).

Results

No adverse reactions were observed after any of the treatments, and none of the topically-treated animals were seen rubbing themselves. The first trichostrongyle eggs were discovered in animals of group D in February, in groups C, O and T in March and in group I in April. The numbers of eggs increased until May and then remained nearly constant in June (Fig 1). The output of trichostrongyle eggs was significantly lower in group I than in the other groups (P<0.01). There were no significant differences with respect to the other nematodes. *Capillaria* eggs were initially abundant in all the groups, but their output soon decreased during the trial, even in the untreated control group. Lungworm larvae were diagnosed in considerable numbers only in April and May, and brainworm larvae occurred only sporadically throughout the trial.

No warbles were found in any of the animals in the treated groups and throat bots in only one animal in group D, whereas all the control animals harboured both warbles and throat bots (Table 1). All the treated groups differed significantly from the control group in this respect (P<0.001).

Weight losses were observed in all the groups between the time of treatment and early April (Table 1) with no significant differences between them. Forty-eight of the 53 calvings recorded were in May and the rest in June, the last on June 17. There was no statistically significant difference in birthweights between the groups although the average birthweight was slightly lower in the control group (Table 1).

Discussion

As an adaptation to the cold climate, winter fur of reindeer is thick and the hair hollow (Timisjärvi and others 1984); the fur might therefore be expected to absorb some of the ingredients of a pour-on preparation, preventing them from penetrating the skin and reaching the circulation. The application technique was therefore modified from that recommended for cattle ('along the top-line in a narrow strip extending from the withers to the tailhead') to try to ensure better contact between the drug and the skin.

All the treatments were 100 per cent effective against warbles, one of the most obvious and probably most harmful groups of reindeer parasites. A slightly lower efficacy against warbles has been reported for subcutaneously administered ivermectin in some cases (Nordkvist and others 1984, Dieterich and Craigmill 1990) but it may be that the sensitivity of detection with respect to solitary larvae was higher in the experiment of Nordkvist and others (1984) owing to the slaughter and necropsy of the animals. Dieterich and Craigmill (1990) suspected that the difficulty experienced in applying the drug because of the low temperature may

TABLE 1: Mean (±sem) number of warbles and throat bots, initial weights, weight losses and calf weights of the groups of reindeer treated with ivermectin

Group	Treatment	Warbles	Throat bots	Weight	Weight loss	Birthweight of calves (kg)	Calf weight Dec 5, 1991 (kg)
				Dec 11, 1990 (kg)	Dec 11, 1990 - April 8, 1991 (kg)		
I	Injection (200 µg/kg)	0	0	82.8 ± 2.1	3.3 ± 1.2	5.51 ± 0.23	51.1 ± 2.4
D	Injection (20 µg/kg)	0	3 ± 3	83.6 ± 1.7	3.3 ± 1.0	5.53 ± 0.17	50.0 ± 1.7
O	Oral (200 µg/kg)	0	0	83.4 ± 1.2	2.3 ± 0.8	5.45 ± 0.30	51.1 ± 1.4
T	Topical (500 µg/kg)	0	0	84.8 ± 1.8	3.4 ± 1.7	5.55 ± 0.25	47.3 ± 2.0
C	None	69 ± 10	21 ± 4	83.4 ± 1.8	2.7 ± 0.8	5.14 ± 0.32	47.3 ± 2.0



have led to underdosing of some animals. The application method which is most susceptible to climatic conditions is probably topical pour-on administration, which on the other hand is probably the easiest method of dispensing ivermectin. The dry weather in the present trial was favourable for topical treatment.

It could be hypothesised that the few warbles surviving ivermectin treatment could give rise to new, more resistant parasites, but current results do not support this idea. Although ivermectin has been used on the Kaamanen herd for almost 10 years, all the treatments in the present trial were 100 per cent effective against warbles and were almost equally effective against throat bots. However, anthelmintic resistance (including to ivermectin) has been detected in several strains of trichostrongyles parasitising domestic ruminants (Björn 1992) and resistance could emerge in reindeer nematodes as well, although the one-treatment-a-year regimen used does not favour the development of resistance.

There were differences between the efficacies of the treatments in combating gastrointestinal trichostrongyle nematodes. The output of trichostrongyle eggs followed a similar spring rise pattern to that observed earlier (Nordkvist and others 1983, Oksanen and others 1992a) a pattern which is most probably caused by delayed (inhibited) development of the nematode larvae. The eggs were first observed in groups D, C, O and T and later in the group I. Ivermectin has been shown to be lethal to both mature and immature (including inhibited) gastrointestinal nematodes in domesticated ruminants (Benz and others 1989) but has also been observed to reduce the reproductive potential of surviving trichostrongyles in lambs (McKellar and others 1988) and reindeer (Nordkvist and others 1984), which makes it difficult to appraise the real fate of nematodes in treated reindeer from faecal examinations. In terms of its anti-trichostrongylid effect, the pour-on administration, in spite of its higher dose, appeared to have only the same level of efficacy as the oral paste formulation and the decimal dose injection, both of which were inferior to the standard injectable administration.

Pharmacokinetic investigations in other ruminant species may explain the differences in efficacy. Scott and others (1990) compared the bioavailability of ivermectin after its oral and percutaneous administration to adult goats. The area under the plasma concentration-time curve (AUC) was significantly larger after oral administration at a dose of 200 µg/kg than after topical administration at 500 µg/kg even though plasma clearance was faster after oral administration. The concentration declined much more slowly in cattle after subcutaneous administration at a dose of 200 µg/kg (Fink and Porras 1989) and the peak concentration observed was almost three times as high as after oral administration to goats. The excretion of ivermectin varies between animal species, so that the clearance times in goats and cattle are not directly comparable. The tissue residues of ivermectin in reindeer were studied by Dieterich and Craigmill (1990), who found the depletion half-life in edible tissues to be slightly longer than that observed in cattle, which in turn is markedly longer than that in sheep (Chiu and Lu 1989). The pharmacokinetics of ivermectin in reindeer after administration by different methods requires further investigation.

The differences in weight changes observed among hinds in different treatment groups during the previous winter (Oksanen and others 1992a) were not observed in this trial. In the earlier experiment, probably because they were pen-fed, all the groups of hinds gained weight, the group injected with ivermectin most of all, followed by the group given the oral paste and the control group. The losses of weight observed in the present experiment were closer to those observed in the field, where the extent and pattern of the weight losses may partly be explained by the antiparasitic agents used, ivermectin having superior efficacy against nematodes (Nordkvist and others 1983). Using organophosphates, Nieminen and others (1980) found no significant difference in the summer weight of calves and their dams treated the previous autumn, whereas Persen and others (1982) demonstrated a greater loss of weight in treated calves during the winter, but increased weight gain later, resulting in higher slaughter weights the following autumn. Nordkvist and others (1984) recorded a significantly smaller weight loss in ivermectin-treated

calves than in untreated calves during the winter, and Heggstad and others (1986) reported that one year after ivermectin treatment of six-month-old reindeer calves they weighed on average almost 3 kg more than untreated animals.

Ivermectin has been shown to be toxic to dung beetles and dipterans (Roncalli 1989) and the practical aspects of the toxicity have been studied extensively in temperate areas such as Britain (Wall and Strong 1987, Jacobs and others 1988), Denmark (Madsen and others 1990), Germany (Barth and Schaper 1991) and the USA (Ewert and others 1991). The results and their interpretations have varied, but the subarctic degradation fauna can be expected to be less tolerant, and therefore, as a better antiparasitic effect is expected with subcutaneously administered ivermectin at 200 µg/kg than with the pour-on preparation at 500 µg/kg, the choice is an easy one: treatment by injection whenever possible, because it makes the best possible use of the active ingredient. The current results do not support the idea of reducing the injection dose, because a reduction would jeopardise the efficacy and increase the risk of resistant nematode strains developing. If injection is difficult to manage, oral administration gives a similar efficacy to the pour-on method, but with only 40 per cent of the amount of active ingredient.

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Influence of route of administration on the plasma concentrations of ivermectin in reindeer

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SUMMARY

The concentration of ivermectin in the plasma of reindeer was measured after it was administered either topically as a pour-on preparation at 500 µg kg⁻¹ bodyweight at different seasons to animals of different ages, or after subcutaneous and oral doses of 200 µg kg⁻¹ bodyweight. The plasma concentrations of ivermectin were highest and least variable after it was administered subcutaneously.

IVERMECTIN is registered in Finland for the treatment of warbles, throat bots and nematodes in reindeer by subcutaneous administration; it is now widely accepted for the treatment of reindeer and more than 80 per cent of the overwintered animals are treated once a year, in early winter (Anon 1993). The proportion of animals treated in Norway and Sweden is slightly lower. The standard procedure is to give one subcutaneous injection of 200 µg kg⁻¹ bodyweight, but Finnish reindeer herders are especially interested in oral and topical application methods, because legislation requires that the injections may only be given by a licensed veterinary surgeon. In Sweden trained reindeer herds men may give ivermectin injections under veterinary control.

The interest in alternative methods of application created a need to investigate the absorption of ivermectin after topical administration to reindeer, a method that has been proved to function well in cattle (Alva-Valdes et al 1986, Eagleson and Allerton 1992) and fallow deer (Rehbein et al 1993). Two trials (A and B) were designed to measure the plasma concentrations of ivermectin after its topical application to different age groups of animals during different seasons of the year.

Recent research (Oksanen et al 1992, 1993) has shown that the antiparasitic efficacy of ivermectin administered subcutaneously at 200 µg kg⁻¹ is superior to that of the same dose administered orally or a dose of 500 µg kg⁻¹ administered topically, at least with respect to seasonally inhibited gastrointestinal nematodes. As this difference probably depends on either the peak levels or the retention times of ivermectin in tissues, a further trial (C) was designed to compare the plasma concentrations after the administration of the drug by the three different routes.

In trial A, four reindeer yearlings (bodyweight 50 to 70 kg) in Kånkämö, Sweden, were treated topically in May with ivermectin (Ivomec Pour-On for Cattle, Merck & Co/Merck Frosst Canada) at 500 µg kg⁻¹ bodyweight along a narrow strip along the back. One animal had fallen and become wet and dirty, so that the drug was applied to wet hide. In addition, a fifth animal was treated in the same way with 833 µg kg⁻¹. Blood was collected on days 0, 2, 7, 14 and 21 and heparinised plasma samples were stored at -20°C until analysis. The concentration of ivermectin was measured by a high-pressure liquid chromatographic method with fluorescence detection (Downing 1989).

In trial B six adult reindeer (1.5 to 12 years old, 60 to 70 kg bodyweight) were treated topically in November, in Dielidasuolo, Norway, with 500 µg kg⁻¹ bodyweight of ivermectin. It had just snowed when the reindeer were treated and they had snow on

them. Plasma samples were obtained on days 0, 4, 7, 14 and 21, and stored at -20°C until analysed by the same method.

For trial C, 15 reindeer calves (nine females and six males, 42 to 54 kg bodyweight) from the Kaamanen reindeer research herd in Finnish Lapland were randomly allocated within sexes into three groups in January. The animals in one group (CI) were treated with Ivomec Injection for Cattle (MSD BV) subcutaneously in front of the left shoulder at a dose rate of 200 µg kg⁻¹, those in the second group (CO) received Ivomec vet paste (Eqvalan paste, MSD BV) on the back of the tongue at a dose of 10 mg and those in the third group (CT) were treated topically with Ivomec Pour-On for Cattle (Merck, Sharp & Dohme BV) on a small area under the hair coating on the back between the shoulder blades ('spot-on') at a dose of 500 µg kg⁻¹. The animals in group CO each received the same dose of 10 mg (equivalent to 200 µg kg⁻¹ for 50 kg) for ease of administration; the mean (SEM) weight of the animals was 48.8 (1.7) kg. The animals were corralled together and blood was collected on days 0, 1, 3, 7, 14 and 20 after treatment. The plasma samples were stored at -20°C before being analysed for ivermectin.

The concentrations of ivermectin were compared by one-way analyses of variance between the groups in trial C and between all the groups when possible (values on days 7 and 14), and if a significant difference was found, the Tukey test was used to examine the difference further. When the analytical results could only be recorded as 'less than' a value, half of this value was used in the calculations. The statistical analyses were made by using the Statistix 3.5 software (Anon 1991).

No adverse reactions were observed in any of the trials. Apart from the animal in trial A that had fallen and become wet and dirty, all the treatments were easy to apply as planned. The maximum concentration of ivermectin in the plasma of the wet animal was markedly lower than that in the other animals in the group. The plasma concentrations in the animal treated with the higher dose (833 µg kg⁻¹) were more than proportionally higher than in the animals in the same trial treated at the normal dose rate.

The plasma ivermectin concentrations in trial C differed significantly between the groups on days 1, 3 and 7 (P<0.001) and 14 (P<0.01) after treatment; the highest values were observed in the group (CI) treated by subcutaneous injection. The concentrations of ivermectin in the topically treated group (CT) in trial C were the lowest in any of the trials, and were significantly lower than in the animals in trials A and B on days 7 (P<0.01) and 14 (P<0.05) (Fig 1).

Animals should be dry and clean when they are treated topically, although the dry snow encountered in trial B did not apparently affect the absorption of ivermectin. The manufacturer advises against the treatment of wet cattle and warns that rain falling on

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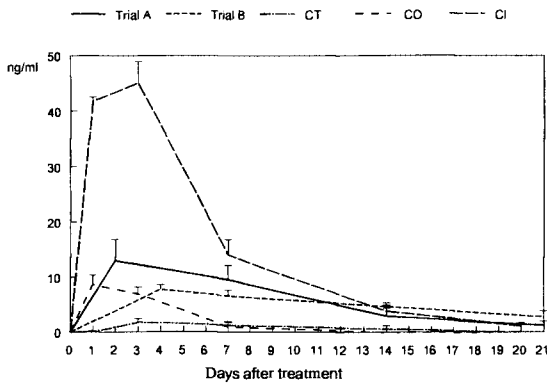


FIG 1: Mean (SEM) plasma ivermectin concentrations in reindeer after the administration of 500 $\mu\text{g kg}^{-1}$ topically (trials A, B and Ct), 200 $\mu\text{g kg}^{-1}$ orally (trial Co) or 200 $\mu\text{g kg}^{-1}$ subcutaneously (Ci)

cattle within two hours of treatment may reduce the efficacy of the treatment. This warning is also relevant to the treatment of reindeer, although reindeer are usually treated during the winter, when the temperature is most often below zero and their coats are dry.

The very low plasma concentrations in the CT group in trial C can be partly attributed to the different characteristics of the pelt during the winter. The reindeer's winter fur is thick and the hair hollow (Timisjärvi et al 1984) and it can therefore be expected to absorb some of the topically applied drug, preventing it from reaching the circulation. Furthermore, the amount of subcutaneous fat might influence the absorption of the drug. The calves in trial C were all in good condition, having been corralled and pen-fed, but the animals in trial B had just prepared for winter. It may be assumed that they also had accumulated a good amount of subcutaneous fat, yet they developed considerably higher plasma levels of ivermectin. It is also possible that the application of the drug to a small area under the hair, as done in trial C in an effort to ensure the best contact with the skin, was a mistake. It is possible that the animals receiving the pour-on drug all the way along the back to the root of the tail may have ingested some ivermectin by grooming. In trial C the animals were treated in a barn at about $+10^{\circ}\text{C}$, while the outdoor temperature was around -10°C . This temperature difference caused some condensation of moisture on to the hairs of the cold animals, but the hair was still only slightly moist. Variations in the absorption of levamisole in relation to season and ambient temperature have also been observed in cattle after its topical application (Taylor et al 1983).

To the authors' knowledge no other reports have been published on the pharmacokinetics of ivermectin in reindeer, but the concentrations in tissues after it had been injected subcutaneously were studied by Dieterich and Craigmill (1990), who calculated tissue depletion half-lives comparable with those in cattle (Chiu and Lu 1989). The peak plasma concentration measured in trial C after subcutaneous injection was of the same order as that measured in cattle (44 ng ml^{-1} , Fink and Porras 1989) but considerably higher than that in red deer in which even a double dose (400 $\mu\text{g kg}^{-1}$) resulted in a peak concentration of 28 ng ml^{-1} (Andrews et al 1993). The difference in the plasma concentrations observed between reindeer and red deer is comparable to that between sheep and goats (Marriner et al 1987, Scott et al 1990), which are phylogenetically closer species. Topical (500 $\mu\text{g kg}^{-1}$) and oral (200 $\mu\text{g kg}^{-1}$) administrations of ivermectin to milking goats were compared by Scott et al (1990), who recorded slightly higher peak plasma concentrations after the oral treatment which declined more rapidly than in the present reindeer study. The concentration in goat plasma after topical application was lower than in the present trials A and B, but much higher than in group CT. Marriner et al (1987) and Bogan and McKellar (1988) reported that iver-

mectin had a higher bioavailability after subcutaneous administration to sheep than after oral administration, matching the present results in reindeer.

The slaughter withdrawal period for ivermectin administered to reindeer in Finland is 56 days, but the present results suggest that the period may not need to be so long for orally treated animals. The withdrawal period for pour-on treatment to reindeer should not be reduced. The slaughter of treated animals in the same winter is exceptional, however, and limited to casualties.

Subcutaneously administered ivermectin was absorbed more readily than ivermectin administered by other routes; thus, that route remains the best for the most effective utilisation of the active ingredient. This conclusion is in agreement with the observed differences in the antiparasitic efficacy of ivermectin administered by different routes.

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Moxidectin as an Endectocide in Reindeer

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Oksanen A, Nieminen M: Moxidectin as an endectocide in reindeer. Acta vet. scand. 1998, 39, 483-489. – During the winter 1991-92, 42 reindeer hinds of the Kaamanen Experimental Reindeer Herd in Finnish Lapland, naturally infected with various parasites, were allocated to 3 groups. One group was an untreated control group and the other 2 groups received either moxidectin or ivermectin at a dose of 200 µg kg⁻¹ subcutaneously. The efficacy of treatment was followed with monthly faecal examinations for nematode eggs and counting of warbles, *Hypoderma tarandi* larvae, and throat bots, *Cephenemyia trompe* larvae, from live animals in spring. The efficacy of moxidectin against warbles (92.8%) and throat bots (70.8%) did not match that of ivermectin, which was 100% against both species. Both moxidectin and ivermectin were effective against gastrointestinal trichostrongylid egg production over the December to May trial period indicating good efficacy against adult and inhibited trichostrongylids. Only non-significant differences were seen in weight development and calf birth weights between the groups. Because of its only moderate insecticidal efficacy, moxidectin cannot be recommended as an endectocide in reindeer.

warbles; throat bots; Hypoderma tarandi; Cephenemyia trompe; trichostrongylids; ivermectin.

Introduction

Reindeer husbandry in northern Finland has used strategic antiparasitic treatment since the late 1970's. First organophosphates administered systemically were used to control warbles (*Hypoderma tarandi* larvae) and throat bots (*Cephenemyia trompe* larvae) and, since the early 1980's, ivermectin has been used (Nieminen 1989). Ivermectin is a synthetic derivative of abamectin, a natural avermectin produced by the actinomycete *Streptomyces avermitilis* (Shoop et al. 1995). Ivermectin has been shown to perform better than organophosphates against these parasites, as well as being efficacious against various nematodes (Nordkvist et al. 1983) and the pentastomid "sinus worm" *Linguatula arctica* (Haugerud et al. 1993). Moxidectin is not an avermectin but a member

of the milbemycin group. It is synthetically derived from nemadectin, a natural macrocyclic lactone fermentation product of the actinomycete *Streptomyces cyaneogriseus* ssp. *noncyanogenus* (Zulalian et al. 1994). Its mode of action is probably similar to that of the avermectins (Shoop et al. 1995). The persistent efficacy of moxidectin was greater than that of ivermectin against ovine trichostrongylids (Taylor et al. 1993) and against induced *Dictyo-caulus viviparus* and *Ostertagia ostertagi* infections in cattle (Hubert et al. 1995, Barth et al. 1997). Avermectins and milbemycins are called endectocides because of their broad spectrum efficacy against both endo- and ectoparasites (nematodes, insects and arachnids). Due to the high nematocidal potency of mox-

idectin, it appears to be a good candidate as an endectocide for use in reindeer as the treatments are done during winter, when nematode parasites of reindeer may be hypobiotic (Nordkvist *et al.* 1984). The aim of the present trial was to evaluate the commercial injection formulation (CYDECTIN® 1% vet inj, American Cyanamid, now Fort Dodge) of moxidectin in reindeer by comparing its antiparasitic efficacy with that of the standard treatment, injectable ivermectin. The differences in animal performance, measured as weight development in the treatment groups as well as the birth and autumn weights of calves born to the groups, were also investigated.

Materials and methods

The trial was initiated on 16 December, 1991, in the Kaamanen Experimental Reindeer Herd (69°09' N, 27°00' E) in northern Lapland. Forty-two adult reindeer hinds marked with individually numbered collars were weighed and allocated to 3 similar groups according to age. The treatment given to each group was drawn by lot. Group C was an untreated control group, group M animals were treated with moxidectin (CYDECTIN® 1% vet inj., Fort Dodge) at a dose of 200 µg kg⁻¹ subcutaneously in front of the left shoulder, and Group I reindeer received ivermectin (IVOMEK® 10 mg/ml vet inj, MSD, now Merial) likewise at 200 µg kg⁻¹. Following treatment, the animals were observed hourly for adverse reactions during 12 h.

The herd was free-ranging in a fell and pine-birch forest area of 1400 hectares, and it was gathered for weighing and sampling monthly until May. When the animals were collected, faecal samples were taken from rectum. The samples were refrigerated and examined as soon as possible, mostly within 4 days after collection.

Faecal egg counts (FEC) were done according

to a modified McMaster method using saturated NaCl solution with 200 g sucrose/litre, each egg counted representing 20 eggs per gram (epg). Nematode eggs were identified as trichostrongylid eggs if they were indistinguishable from those of the family Trichostrongylidae: oval or ellipsoid, not markedly asymmetrical, thin-shelled and length 60 to 100 µm, to the genus *Capillaria* if they were rough-shelled, dark-stained, of barrel shape, length about 50 µm, and with slightly protruding polar plugs, or to the genus *Skrjabinema* if they were typical to the genus: about 50 to 70 µm long, thin-shelled and markedly asymmetrical (like an orange section). For statistical treatment, all the trichostrongylid faecal egg count values from each individual from January to May were summed up and the sum was divided by the number of samples (5) to get an individual faecal egg count mean value (FECM).

Warbles were counted on May 12 by visual examination and digital palpation. When the amount of warbles exceeded 30, the count was done in tens, because adjacent warbles might blend together and prevent exact enumeration. Throat bots were counted on May 12 endoscopically using a bronchoscope designed for humans (Oksanen *et al.* 1992b). The amount seen was estimated to the nearest 5 if it exceeded 25. The hinds were weighed using an ovine balance modified to enable the weighing of reindeer (1 kg reading intervals). The new-born calves were weighed within 24 h of birth (spring balance, 100 g intervals). Calves were also weighed in autumn 1992 to elucidate the survival and growth.

Reductions in the respective parasite burden were calculated from the geometric means of parasite numbers in the treated groups compared to the control group, applying the World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines (Wood *et al.* 1995). The significance of difference in num-

bers of warbles and throat bots, as well as in FECMs between the groups was tested in Kruskal-Wallis one-way analysis of variance. Weight gain differences were statistically tested using the one-way analysis of variance. All statistical analyses were carried out with the Statistix 4.1 analytical software package (Anon. 1994).

Results

No adverse reactions could be noticed following either of the treatments. During the trial, one animal of the group M died due to a cause unrelated to the trial, and one animal of the group C disappeared leaving no trace. Trichostrongylid eggs were on December 16 (day 0) recorded in low numbers (max. 200 epg) from almost half of the animals in all the groups. The average trichostrongylid FEC remained positive in the control animals throughout the experimental period with peak values (~170 epg and ~90 epg) in March and May. After treatment the trichostrongylid FECs became negative in the groups M and I. Subsequently (mostly only after March) they increased at a much slower rate than those of the control group (Fig. 1). The FECMs were significantly different between the groups ($p < 0.001$) (Table 1), with both the treatments causing >90% reduction.

Both moxidectin and ivermectin appeared to reduce *Capillaria* egg production, but the difference in the egg counts was not significant. The geometric mean of *Capillaria* egg counts also in the control group remained mostly below 2 epg. *Skrjabinema* eggs were seen in April and May in small numbers in the faeces of a few animals belonging to all of the groups.

In the control group, 12 hinds out of 13 harboured warbles (median intensity 50, range 8-120). Moxidectin clearly had efficacy against them (8 of 12 infected, median intensity 4, range 2-11). No warbles were found in any of

the ivermectin treated animals. The difference in the number of warbles between the groups was statistically significant ($p < 0.001$). In comparison of the mean warble ranks, group C differed ($p < 0.05$) from groups M and I.

All 13 of the control group hinds harboured throat bots (median intensity 13, range 2-35). Nine of 12 moxidectin treated animals were infected (median intensity 5.5, range 1-15). No throat bots were found in any of the ivermectin treated animals. The difference in the number of throat bots between the groups was statistically significant ($p < 0.001$); the mean throat bot rank of the I group differed from the other 2 groups.

The mean weight gain between day 0 and day 130 (April 24) was highest and the calf birth weight lowest in the untreated group, however, the difference between the groups was not significant (Table 2). One animal of the group C gained 17 kg and one of the group I lost 11 kg. These 2 animals had a large influence on the mean and s.e.m. for their respective groups.

Discussion

During the trial winter, trichostrongylid egg output differed from that experienced in other years in the same herd (Oksanen *et al.* 1992a, 1993, Oksanen 1996) in that at the beginning of the trial in December many animals excreted eggs. The egg output of the untreated control group also never reached zero. In March, there was an astounding peak in trichostrongylid egg output of the control group (Fig. 1). There is no readily available good explanation for that.

Moxidectin has been found to be highly efficacious against the most important nematode parasites of cattle and sheep (Ranjan *et al.* 1992, Taylor *et al.* 1993), as has ivermectin (Campbell & Benz 1984). In the present trial, both moxidectin and ivermectin showed high efficacy against trichostrongylids in reindeer.

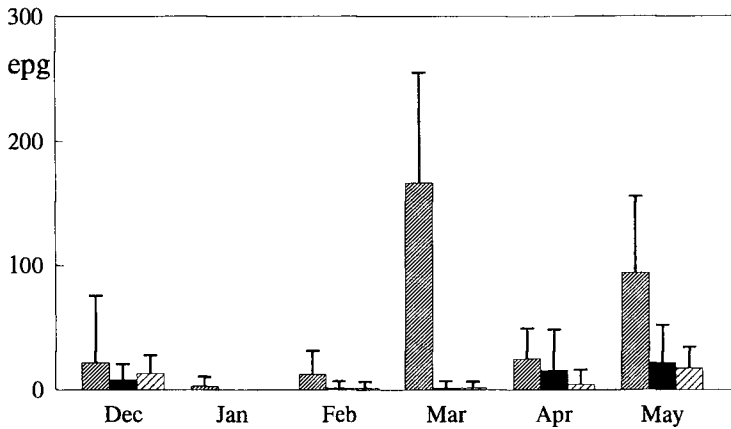


Figure 1. Mean (standard deviation of the mean) of trichostrongylid egg output of Kaamanen reindeer hinds of control and moxidectin and ivermectin treatment groups, sampled monthly from December 1991 to May 1992. ▨ Control, no treatment. ■ Moxidectin subcutaneously 200 µg kg⁻¹ on December 16. ▩ Ivermectin subcutaneously 200 µg kg⁻¹ on December 16.

Injectable moxidectin was in one trial 96% effective against first stage larvae of the ovine nasal bot fly *Oestrus ovis*, but the efficacy against second and third stage larvae was 100% (Puccini *et al.* 1994). At the time of treatment in the present trial, obviously all the *C. trompe* were 1st stage larvae (Nilssen & Haugerud 1995) and thus perhaps least susceptible to treatment, which might have contributed to the low (70.8%) efficacy.

Moxidectin has also been reported to have high efficacy against cattle warbles (Scholl *et al.* 1992, Lonneux & Losson 1994). In the present trial the efficacy of moxidectin injection against reindeer warbles was 92.8%, which is at the same level as the efficacy of the organophosphate fenthion (Nordkvist *et al.* 1983). This efficacy might be considered substantial. However, as ivermectin in the present trial, and also in many other experiments (Nordkvist *et al.* 1983, Oksanen *et al.* 1992a, 1993, Oksanen 1996) killed 100% of warbles, moxidectin is definitely not the first choice endectocide. In two trials with horses, oral moxidectin was less efficient against *Gasterophilus* spp. larvae than

oral ivermectin (Xiao *et al.* 1994, Monahan *et al.* 1996). While abamectin injection had high efficacy against biting lice, *Bovicola bovis*, no effect was seen following moxidectin injection (Titchener *et al.* 1994). The dung from moxidectin treated cattle was also less toxic to various insects than the dung from ivermectin treated cattle (Strong & Wall 1994). Therefore, it has been claimed that the anthelmintic and acaricidal properties of moxidectin are generally superior to its insecticidal properties (Shoop *et al.* 1995).

Whether the unsatisfactory efficacy against warbles and throat bots depends solely on the intrinsic lower efficacy of moxidectin against insects, cannot be stated. Moxidectin is also more lipophilic than ivermectin (Hayes 1994), and reindeer during the winter are generally on a negative energy balance consuming their fat reserves. Therefore, it seems possible that another reason for the inadequate efficacy might be in the pharmacokinetics of moxidectin in weight-losing reindeer. Pharmacokinetics of moxidectin in reindeer should be examined before conclusions can be drawn. The efficacy of

Table 1. Geometric means and efficacy of endectocide treatment against various parasites in Kaamanen reindeer hinds 1991-92. The number of *Hypoderma tarandi* and *Cephenemyia trompe* counted in live animals.

Parasite	Group ^a		
	Control	Moxidectin	Ivermectin
<i>Hypoderma tarandi</i>	39.3	2.85	0
% reduction	—	92.8	100
<i>Cephenemyia trompe</i>	13.7	4.0	0
% reduction	—	70.8	100
Trichostrongylid FECM ^b	56.3	4.3	2.8
% reduction	—	92.3	95.1

^a Control, no treatment. Moxidectin 200 µg/kg on December 16. Ivermectin 200 µg/kg on December 16.

^b Faecal Egg Count Mean = (FEC(Jan) + FEC(Feb) + FEC(Mar) + FEC(Apr) + FEC(May))/5.

Table 2. Weights (kg) of the reindeer hinds and their calves of the control and treatment groups in Kaamanen 1991-92.

	Group ^a		
	Control	Moxidectin	Ivermectin
Weight Day 0 ^b	75.4 (1.9); 13 ^c	76.9 (2.8); 13 ^c	78.1 (2.8); 14
Growth to Day 130	1.8 (1.5); 13	1.0 (0.8); 13	0.8 (1.3); 14
——— ^d	0.5 (0.9); 12	1.0 (0.8); 13	1.7 (1.0); 13
Calf birth weight	5.24 (0.21); 10	5.55 (0.25); 12	5.63 (0.29); 11
Calf weight Sep 18 ^e	48.9 (3.4); 7	50.2 (2.1); 11	47.6 (1.7); 10
Calf weight Dec 14 ^f	42.5 (2.5); 6	46.6 (2.4); 8	45.3 (1.5); 9

^a Control, no treatment. Moxidectin 200 µg/kg on December 16. Ivermectin 200 µg/kg on December 16.

^b Mean (standard error of the mean); number.

^c The eventually missed two animals excluded.

^d Omitting the two extreme values (see text).

^e All calves were not found in September due to the herd being spread.

^f Some calves were slaughtered in November (normal procedure for the herd).

moxidectin in fattening reindeer in early autumn against warbles and throat bots might also be worth evaluating.

Although the mean weight gain of untreated control animals was highest, this may at least partly be caused by parasite biomass. Typically, a third instar warble weighs 1600 mg (Breyev 1961) and it is associated with host tissue reaction. Nordkvist (1967) estimated that warbles alone could make up to 500 g in one animal. After removal of 2 animals with extreme weight

gain or weight loss, there is a weak positive effect of treatment in both weight gain and calf birth weight.

Acknowledgements

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Sammendrag

Moxidectin som endektosid i rein.

I desember 1991 ble 42 reinsdyrsimler fra Kaamanen forsøksflokk delt i tre grupper. En gruppe var ubehandlet, mens de to andre gruppene ble behandlet subkutan enten med moxidectin eller ivermectin med dose 200 µg kg⁻¹. Effekten av behandlingen ble vurdert etter månedlige fæcesundersøkelser for nematode-egg til mai (1992) og etter telling av hud- og nesebrenslarver (*Hypoderma tarandi* og *Cephemyia trompe*). Moxidectin hadde lavere effekt mot hud- og nesebrenslarver (92.8% respektive 70.8%) enn ivermectin (100% mot begge arter). Både moxidectin og ivermectin hadde høy effekt mot eggproduksjon av gastro-intestinale trichostrongylider, hvilket indiserer høy effekt mot både voksne og inhiberte trichostrongylider. Det var ikke signifikante forskjell mellom vektutvikling hos simler eller fødselsvekter hos kalver.

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SHORT COMMUNICATION

Larvicidal effectiveness of doramectin against natural warble (*Hypoderma tarandi*) and throat bot (*Cephenemyia trompe*) infections in reindeer

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Key words. *Hypoderma tarandi*, reindeer warble fly, *Cephenemyia trompe*, reindeer throat bot fly, *Rangifer tarandus*, reindeer, doramectin, avermectin.

Warbles (*Hypoderma tarandi* (L.) larvae) and throat bots (*Cephenemyia trompe* (Modeer) larvae) (Diptera: Oestridae) are common parasites of both the semi-domesticated reindeer, wild reindeer and caribou (Bennett & Sabrosky, 1962; Helle, 1980; Thomas & Kiliaan, 1990). As they belong integrally to the ecosystem the reindeer live in, it is difficult to quantify the cost of these parasites to reindeer husbandry. However, 15–20% of the production income was estimated to be consumed by warbles and throat bots in Sweden (Nordkvist, 1967). In Russia, even higher costs, 25–30%, have been claimed to be caused by warbles alone (Saval'ev, 1968). Ivermectin is, so far, the only avermectin recommended for use in reindeer. It has been observed to have high efficacy (reaching 100%) against both reindeer warbles and throat bots (Nordkvist *et al.*, 1983, 1984; Dieterich & Craigmill, 1990; Oksanen *et al.*, 1993). Doramectin is a novel avermectin which has been reported to have 100% efficacy against first, second and third instars of cattle warbles, *Hypoderma bovis* (Hendrickx *et al.*, 1993), besides being highly effective against various nematode parasites in cattle (Yazwinski *et al.*, 1994). The purpose of the present trial was to evaluate the efficacy of doramectin (Dectomax®, Pfizer, Sandwich, U.K.) against reindeer warbles and throat bots.

On 20 December 1994, at the Kaamanen Reindeer Research Herd in Finnish Lapland, thirty-six adult female semi-domesticated reindeer, 1.5–11.5 years old, were randomly (by lot) assigned to either the saline or doramectin group. In addition, four male 1.5-year-old reindeer were also randomly assigned to the groups. Infections could not be demonstrated at the time of allocation, because the parasites are at the first or early second instar stage of development. However, a high prevalence of natural infections with both warbles and throat bots was expected based on earlier trials within the herd (Oksanen *et al.*, 1992a, 1993). The animals were individually marked

and weighed. Animals of the saline group were given a subcutaneous injection in front of the left shoulder with sterile physiological saline solution at a rate of 0.2 ml/10 kg, whereas those of the doramectin group received doramectin at a rate of 0.2 mg/kg in the same place. The dose was that registered for cattle, which is similar to the dose of ivermectin both for cattle and reindeer. All animals were examined for adverse reactions for 2 h following treatment. After that, the reindeer were freed to graze with the rest of the herd. The winter pasture was a fenced fell and forest area of about 1400 hectares. The reindeer were rounded up monthly for routine weighing. On 28 April (day 129 post treatment), the animals were examined for warbles visually and by digital palpation. Throat bots were visualized using an endoscope as described earlier (Oksanen *et al.*, 1992b). Briefly, a fibre-optical human bronchoscope was inserted via the left nostril to the pharynx to enable a view to the dorso-medial tonsil sac, where the second and third instars live (Rehbinder & Nordkvist, 1983). Larvae of both species were counted. When the number of warbles exceeded thirty, the count was done in tens, because adjacent warbles might blend together and prevent exact enumeration. Likewise, the number of throat bots was also rounded off to the nearest five if it exceeded twenty-five.

The efficacy of the treatment was calculated according to the formula:

$$\% \text{ Efficacy} = \frac{a/c - b/d}{a/c} \times 100$$

where a = number of infested reindeer in the saline group; c = total number of reindeer in the saline group; b = number of infested reindeer in the doramectin group; d = total number of reindeer in the doramectin group. Statistical analysis was performed using the chi-square test (Yates' continuity correction).

No adverse reactions were seen in any animals following treatment. One hind of the saline group died in February due to peritonitis that was considered unrelated to the experiment. All but one of the nineteen surviving saline group animals harboured both warbles and throat bots when examined in late

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Table 1. Arithmetic mean number (SD) of *Hypoderma tarandi* and *Cephenemyia trompe* counted in saline-treated and doramectin-treated groups 129 days post treatment.

Group	No. of animals examined	<i>Hypoderma tarandi</i>	<i>Cephenemyia trompe</i>
Saline	19	78 (52)	38 (28)
Doramectin	20	0	0

Table 2. *Hypoderma tarandi* and *Cephenemyia trompe* infested and non-infested reindeer in saline-treated and doramectin-treated groups 129 days post treatment.

Group	Infested animals*	Non-infested animals
Saline	18	1
Doramectin	0	20

Yates' corrected chi-square 31.48 ($P < 0.001$).

*All animals infested with both species.

April (Table 1). None of the doramectin group animals were infested with either of these parasites ($P < 0.001$), the efficacy of treatment being 100% (Table 2).

The avermectins have a superior efficacy against both *H. tarandi* and *C. trompe* when compared with organophosphates that were in common use before ivermectin (Nordkvist, 1967; Nordkvist *et al.*, 1983). The complete efficacy against warbles and throat bots now observed with doramectin and previously with ivermectin confirms the high sensitivity of these parasitic insect larvae to the avermectin group of macrocyclic lactones. Avermectin use in reindeer is enhanced by the effectiveness against nematode parasites. The nematocidal efficiency of ivermectin is well documented in reindeer (Nordkvist *et al.*, 1983; Oksanen *et al.*, 1993). Gastrointestinal nematodes have been shown to depress food intake in reindeer in late winter and spring (Arneberg *et al.*, 1993) and nematode control has increased weight gain of female reindeer during winter (Oksanen *et al.*, 1992a). The efficacy of doramectin against reindeer nematodes still remains to be tested.

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Influence of timing of endectocidic antiparasitic treatment on its efficacy in overwintering reindeer

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Abstract: To find out if timing of endectocidic antiparasitic treatment is critical for its efficacy in overwintering reindeer, 72 hinds of the Kaamanen Experimental Reindeer Herd were randomly allocated to four groups. Three groups received ivermectin mixture orally once at a dose of 200 µg/kg, either in September, December, or February, and one group was left untreated. Antiparasitic efficacy was evaluated by counting *Hypoderma tarandi* and *Cephenemyia trompe* larvae in April, and by faecal examination for trichostrongylid nematode eggs in March and April. Production efficacy consequences were assessed by comparing animal weight development from November to April, and calf birth weights. No difference could be seen in the antiparasitic efficacy of the treatments; all were 100 % efficient against *H. tarandi* larvae (warbles) and *C. trompe* larvae (throat bots), and reduced the trichostrongylid egg output by 62 to 74 %. Weight gains of the groups were not significantly different, however the calf birth weights differed nearly significantly ($P = 0.057$). On average, smallest calves were produced by the untreated group.

Key words: ivermectin, avermectin, warbles, throat bots, trichostrongylids, *Hypoderma tarandi*, *Cephenemyia trompe*, *Rangifer tarandus*.

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Introduction

Endectocidic antiparasitic treatment (efficacy against both some endo- and ectoparasites) has become a routine in Finnish reindeer husbandry (Anon., 1993). The goal is to help animals to survive the critical winter period and increase their fitness, thereby aiding them to produce healthy offspring. From the endectocidic avermectins and milbemycins produced, the only one so far in commercial use in reindeer is ivermectin. Injectable ivermectin at a dose of 200 µg/kg has high efficacy against warbles, *Hypoderma tarandi* (Diptera: Oestridae), and throat bots, *Cephenemyia trompe* (Diptera: Oestridae), the «sinus worm» *Linguatula arctica* (Pentastomida), and many nematodes parasitizing reindeer (Nordkvist *et al.*, 1983, 1984; Haugerud *et al.*, 1993). Oral ivermectin at the same dose given in December was also highly effective against warbles and throat bots, but its nematocidal efficacy was lower than that of the injection (Oksanen *et al.*, 1992a, 1993).

It has been observed that different developmental stages of parasitic nematodes have different susceptibilities to antiparasitics. In general, hypobiotic (inhibited) larvae with minimal metabolism are regarded as those most resistant (Soulsby, 1982). Whereas in examination 50 days later it was found that all abomasal nematodes had been killed after ivermectin injection on 23 February (Nordkvist *et al.*, 1983), no efficacy was seen after injection given

on 25 November, as measured 147 days post treatment (Nordkvist *et al.*, 1984). While the apparent lack of efficacy might also have been caused by reinfection during the winter, the authors considered seasonally inhibited development of the nematodes to be the most probable reason. Different stages of insect parasites may also have variable susceptibility to antiparasitics; first instars of *Oestrus ovis* (Diptera: Oestridae) of sheep were less susceptible to moxidectin (another endectocide) than were 2nd and 3rd instars (Puccini *et al.*, 1994).

As antiparasitic treatment of reindeer is in practice only possible in connection with the separation of animals to live over winter from those to be slaughtered, the treatments are sometimes spread throughout the slaughter season from September up to February, whenever weather and snow conditions allow the flock to be rounded up. Therefore, the oestrid fly parasites can be either 1st or 2nd instars during the treatment (Bergman, 1917; Nilssen & Haugerud, 1995), and the seasonal hypobiosis of nematodes can be either early, intermediate, or late.

According to earlier studies (Oksanen *et al.*, 1992a, 1993), differences in nematocidal efficacy only become evident in spring when hypobiotic gastrointestinal nematode larvae mature and the infections become patent. Faecal examinations are therefore to be performed in the spring. The aim of the present study was to examine if timing of the endectocidic treatment has influence on its efficacy.

Materials and methods

On 26 September, 1995, 72 hinds of the Kaamanen Experimental Reindeer Herd (69°09' N, 27°00' E) were randomly allocated according to age to four similar groups of 18 animals each. Group 1 was left untreated as controls, and the groups 2 to 4 received ivermectin (Ivomec® vet. 0.8 mg/ml mixt., Merck Sharp & Dohme B. V., Holland) orally at a dose of 200 µg/kg once on 26 September, 19 December, or 16 February. Due to not finding all the animals allocated to the specified group at the time of the scheduled treatment or later, the final group sizes were: 16 hinds in groups 1 and 2, 17 in group 3, and 18 in group 4, respectively.

Warbles were counted visually and by digital palpation on 24 April, and throat bots at the same time using a human fibre-optic bronchoscope according to the method described earlier (Oksanen *et al.*, 1992b). When the number of warbles exceeded 30, the count was done at tens, as adjacent warbles

might blend together and prevent exact enumeration. Likewise, the number of throat bots seen was estimated to the nearest five when exceeding 25. Rectal faecal samples were collected on 16 February, 25 March, and 23 April. They were examined according to a modified McMaster method, each egg representing 20 eggs per gram (epg). The animals were weighed (to the nearest kg) on 26 September, 02 November, 23 April, and immediately before treatment using a digital scale based on "The Poldenvale Lambway" (Precision Weighers, Reading, England). New-born calves were weighed within 24 hours after birth (0.1 kg precision).

For statistical analysis of trichostrongylid nematode egg counts, differences were assessed by calculating individual arithmetic means (Faecal Egg Count Mean, FECM) of the egg counts during the spring (25 March and 23 April). The FECMs were compared between the groups by one way analysis of variance. Individual weight gains (from November to April) and calf birth weights were similarly compared. The statistical analyses were performed using the Statistix® 4.1 software package (Analytical Software, 1994). Treatment efficacy was calculated from the trichostrongylid FECMs according to the following formula (modified from Wood *et al.*, 1995):

Treatment efficacy of group *i* =

$$\frac{\text{geometric mean of FECM in group 1} - \text{geometric mean of FECM in group } i}{\text{geometric mean of FECM in group 1}} \times 100 \%$$

Corresponding formula was used to calculate treatment efficacy against warbles and throat bots.

Results

All of the untreated animals (group 1) harboured *H. tarandi* larvae. Most of them (12 out of 16) were also infected by *C. trompe* larvae (Table 1) None of the ivermectin treated reindeer (groups 2 to 4) had any of these parasites, so the efficacy of all the treatments was 100 % against oestrid fly larvae. On 16 February, the trichostrongylid nematode egg count was zero in all others, but one animal of the untreated group excreted a small number of eggs (20 epg). Subsequently, the nematode FECM of the untreated group (group 1) was highest, but the difference between the groups was not significant ($P = 0.12$). The FECMs of the treated groups were closely similar (Table 1).

Table 1. Warbles (*Hypoderma tarandi* larvae) and throat bots (*Cephenemyia trompe* larvae), trichostrongylid nematode faecal egg count means, start weights, weight gains, and calf birth weights of the groups of reindeer hinds, treated orally with ivermectin at 200 µg/kg at different times, or untreated.

Group	1	2	3	4
	untreated	treated Sep 26	treated Dec 19	treated Feb 16
<i>n</i>	16	16	17	18
<i>H. tarandi</i> ^a	52.9 (36.0)	0	0	0
- treatment efficacy		100 %	100 %	100 %
<i>C. trompe</i> ^a	14.9 (12.4)	0	0	0
- treatment efficacy		100 %	100 %	100 %
FECM ^b	12.9	4.8	4.0	3.3
- treatment efficacy		62 %	69 %	74 %
Start weight ^c	79.0 (13.1)	80.1 (10.0)	78.9 (10.9)	80.0 (10.1)
Weight gain ^d	-0.1 (5.6)	-0.2 (5.4)	1.6 (4.8)	-2.6 (4.7)
Calf birth weight ^e	5.7 (0.9), 14	6.2 (1.0), 13	6.6 (0.8), 13	6.4 (1.0), 13

^a mean number (standard deviation).

^b geometric mean of individual Faecal Egg Count Means (25 March and 23 April), epg.

^c weight 02 November (standard deviation), kg.

^d weight 23 April - weight 02 November (standard deviation), kg.

^e birth weight (standard deviation), kg, *n*.

Weight gain/loss of the groups of hinds varied between a loss of 2.6 kg and a gain of 1.6 kg. The differences were not statistically significant ($P = 0.14$). Difference in birth weights was nearly significant ($P = 0.057$), and the calves born to the untreated group were on average smallest.

Discussion

Due to the 100 % efficacy against both warbles and throat bots, the present results cannot suggest if different developmental stages are equally susceptible or not. The efficacy of all the treatments against trichostrongylid egg production was higher than expected for orally administered ivermectin from earlier studies. In the study of Oksanen *et al.* (1993), the efficacy of oral treatment against FECM at the corresponding time was 47 %, while that of injection treatment at the same dose was 86 % (data not shown). Although the difference in egg output between the groups in the present study was not significant, the nevertheless substantial efficacy raises the question, if the oral mixture designed for sheep used in this study might be better absorbed than the equine paste used in the earlier studies. In sheep, it has been observed that the bioavailability of intra-abomasally administered ivermectin is vastly higher than that of the drug placed intraruminally (Prichard *et al.*, 1985). In case some of the oral mixture passes on directly into the abomasum, its bio-

availability could be consequently higher than that of the equine paste that is probably being mixed in the tuminal contents. This point deserves further pharmacokinetic studies.

Decrease in faecal egg counts does not definitively prove a proportional change in worm burdens, as nematode egg production is affected by many factors. Also ivermectin treatment is shown to suppress the fecundity of surviving nematodes (McKellar *et al.*, 1988). However, that suppression was documented 7 and 14 days after treatment, when measurable ivermectin concentrations still exist in animal tissues (Bogan & McKellar, 1988). In the present study, the time between treatment and the start of the FECM examination was 5 weeks (group 4) to 25 weeks (group 2). In case the reduction of fecundity caused by ivermectin is temporary, it might already have subsided before the FECM examination.

Trichostrongylid egg production has earlier been observed to be discontinued for the winter period (Oksanen *et al.*, 1992a, 1993). This was seen also in the present study in the mostly zero egg counts on 16 February, and is most probably caused by the seasonal hypobiosis of the worms.

The weight development figures shown are based on weighing in November, as many animals were missing from the September weighing. No difference was seen in the weight development (of those present in September) from September to November between the groups (data not shown).

From the practical point of view it appears that parasites can be effectively treated anytime during the winter. The statistically nonsignificant and small differences in weight gain/loss and in birth weights indicate, assuming comparable parasite fauna and good winter pastures, that the timing of endectocide treatment of reindeer hinds is not very critical. Although not quite significant, the average birth weight of the calves of the untreated group was lowest, which is concomitant with earlier observations (Nieminen, 1989), supporting the assumption of the benefit of treatment.

If first quality hides are desired, it must be noticed that warbles can cause damage already in October–November (Nieminen, 1992). Even though the larvae were subsequently killed, the damage may persist during subsequent years in the form of scars. Therefore, early treatment might be preferable.

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Ivermectin treatment did not increase slaughter weight of first-year reindeer calves

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Abstract

To investigate if antiparasitic treatment of reindeer calves during the summer could increase their carcass weight during the slaughter period in autumn and winter, 529 reindeer calves were allocated to three groups, weighed, and marked with individually numbered plastic ear tags in early July, 1995. One of the groups was left untreated, another was treated with ivermectin injection at 200 µg/kg, and the third with pour-on ivermectin at 500 µg/kg. Following slaughter, carcass weights were received from 231 animals, and there was no difference between the treatment groups. © 1998 Elsevier Science B.V.

Keywords: Reindeer; Meat production; Ivermectin; Parasitosis

1. Introduction

Parasitism is ubiquitous in livestock and affects especially young individuals. Parasite control with anthelmintics is therefore considered an integral part of management of grazing young cattle. Reindeer calves pick up parasite larvae at an early age; born mostly in May, many calves harboured patent gastro-intestinal nematode infections when examined in late June or early July (Oksanen et al., 1990). They may also get heavy warble (*Hypoderma tarandi*) and throat bot (*Cephenemyia trompe*) (both Diptera: Oestridae) infections during their first summer (Helle, 1980; Rehbinder and Nordkvist, 1984; Folstad et al., 1989).

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To increase production, reindeer-herding methods have changed considerably during the last few decades in Finland. Perhaps the most important changes have been the increased supplementary winter feeding (Nieminen and Autto, 1989; Valmari, 1993) (which helps to sustain more animals) and the increased slaughter of reindeer calves (Kojola and Helle, 1990); the winter flock now consists mainly of adult pregnant females. While the summer pastures could sustain more reindeer in most districts, the winter pastures are limited (Kumpula et al., 1997). Antiparasitic treatment has also become a routine; over 80% of overwintering reindeer are treated once yearly with ivermectin (Anon, 1993). Ivermectin is a so-called 'endectocide,' having efficacy against both endo- and ectoparasites (nematodes and arthropods). Slaughter of animals in early winter and antiparasitic treatment of the remainder virtually eliminate the problems of clinical parasitism caused by warbles and throat bots, and probably also reduces problems associated with nematode infections. Although winter ostertagiosis is not recognised as a clinical disease in reindeer, maturation of hypobiotic larvae in late winter or early spring (Nordkvist et al., 1984; Oksanen et al., 1993) reduces appetite and this reduction can be prevented by ivermectin treatment (Arneberg et al., 1996). Ivermectin treatment in early winter has increased the growth of half-year-old reindeer calves during the subsequent year (Heggstad et al., 1986). About 80% of slaughtered reindeer in Finland are first-year calves (Anon, 1996), and increased calf growth rates during summer and autumn leading to higher carcass weights would therefore be highly desirable.

Hides have now got a relatively high commercial value to the reindeer owner (about FIM 50 to 55, ~ECU 9) each for first-quality hides, and FIM 10 less for warbled ones (Lapin Turkisjaloste Ky, oral comm.). If reindeer calves are slaughtered early (i.e. before December), warbles are usually not a problem. Sometimes, climatic conditions cause difficulty in collecting the flocks, the slaughter is delayed, and warbles reduce hide quality and value by making breathing-holes through the backskin (Nieminen, 1992). The infection intensity of reindeer warbles can be high, commonly reaching 150 to 200 warbles per animal (Breyev, 1961). Ivermectin has several weeks of residual efficacy against bovine lungworms and other nematodes (Barth, 1983; Armour et al., 1985). As larvae of *H. tarandi* are very susceptible to ivermectin (Haugerud et al., 1993; Oksanen et al., 1993), an analogous residual efficacy of unknown length might be expected against these larvae too. The flight and egg-laying season of *H. tarandi* females is principally in July and August, although it may continue till September (Bergman, 1916; Hadwen, 1926; Saveljev, 1968). If the summer ivermectin treatment could prevent infections during July–August, a reduction in warble numbers might follow ensuring a higher value of hides.

In a preliminary trial performed in the Kaamanen Experimental Reindeer Herd in Finnish Lapland in June–December 1994, the live-weight gain of ivermectin-treated male calves was significantly higher than that of untreated ones. No difference was, however, seen for female calves (Oksanen and Nieminen, 1995).

Our principal aim in the present trial was to investigate if increase in slaughter weight can be achieved under field conditions. We also tried to find out if summer ivermectin treatment reduces warble infection.

2. Materials and methods

The mean carcass weight of reindeer calves (about half-year-old) in Finland in 1990 to 1995 was estimated to be about 22 kg (SD 2) (M. Nieminen, unpubl.). As reindeer carcass price is about FIM 28 per kg, we concluded that at least an increase of 1 kg in slaughter weight would be economically important, and this is equal to 0.5 SD. We wanted a high probability to detect the possible effect, so we required 90% power. The significance level was set to 1%. Using the nomogram of Altman (1991), the group size required to fulfil these preconditions is 125 animals. As we wanted to try both the ivermectin injection and pour-on (that reindeer owners are allowed to administer themselves), we needed three groups. Therefore, this experiment required a minimum of 375 calves.

The trial was performed in 1995 at two volunteer reindeer-herding co-operatives: Palojärvi (PJ) and Kemin-Sompio (K-S) (Fig. 1), located in the forest area of Lapland. Both the co-operatives are relatively typical to the central part of the Finnish reindeer husbandry area with coniferous forests and marshland, but somewhat more productive than the average, as seen from the following figures. There are 322 reindeer owners at PJ and 195 at K-S. The number of live reindeer (overwintering herd) is very close to the maximum number allowed by authorities; PJ: 4963 of 5000 (99.3%), K-S: 12945 of 13000 (99.6%), total in Finland (FIN) 208140 of 228900 (90.9%). The calf percentage (calves produced by 100 adult hinds, counted in autumn or winter round-ups) was PJ: 73, K-S: 84, FIN: 69 during the herding year 1994–95 (Anon, 1996). In an inventory of winter lichen pastures, the pastures of K-S were recorded as fair, but those of PJ as poor (Kumpula et al., 1997).

During the standard calf ear marking (incision of the owner's mark) on 3–4 July (PJ, 237 calves) and 4–5 July (K-S, 292 calves), the calves were weighed on a standard bathroom balance to the nearest kg, ear-tagged with individually numbered (but otherwise similar) plastic tags, and systematically allocated in the order of marking (with a random starting point) to three groups. Group 1 was untreated (no placebo given), Group 2 animals received Ivomec[®] Injection for Cattle (Merck, Sharp and Dohme B.V., Haarlem, Netherlands) subcutaneously in the left mid-cervical area at a dose rate of 200 µg/kg, and Group 3 was treated topically with ivermectin (Ivomec[®] Pour-On for Cattle; MSD B.V., Haarlem, Netherlands) on the midline of the back from the neck to the sacrum at a dose of 500 µg/kg. Following treatment, the calves were released to follow their dams until the autumn and winter round-ups and slaughter. The herders were not informed about the composition of the treatment groups.

During the October-to-January round-ups, those of the calves chosen to live (replacements) were registered as such, while carcass weight was recorded from those slaughtered. These data were collected by the herding co-operatives. We counted warbles only from the 8 animals slaughtered in January, because they were not reliably apparent earlier.

Statistical analyses were performed using Statistix[®] 4.1 software package (Analytical Software, 1994), and consisted of Student's *t*-test, χ^2 test, and the Mann–Whitney test. One-way analysis of covariance was done with BMDP software (BMDP Statistical Software Inc., Los Angeles, CA), having *Carcass weight* as the

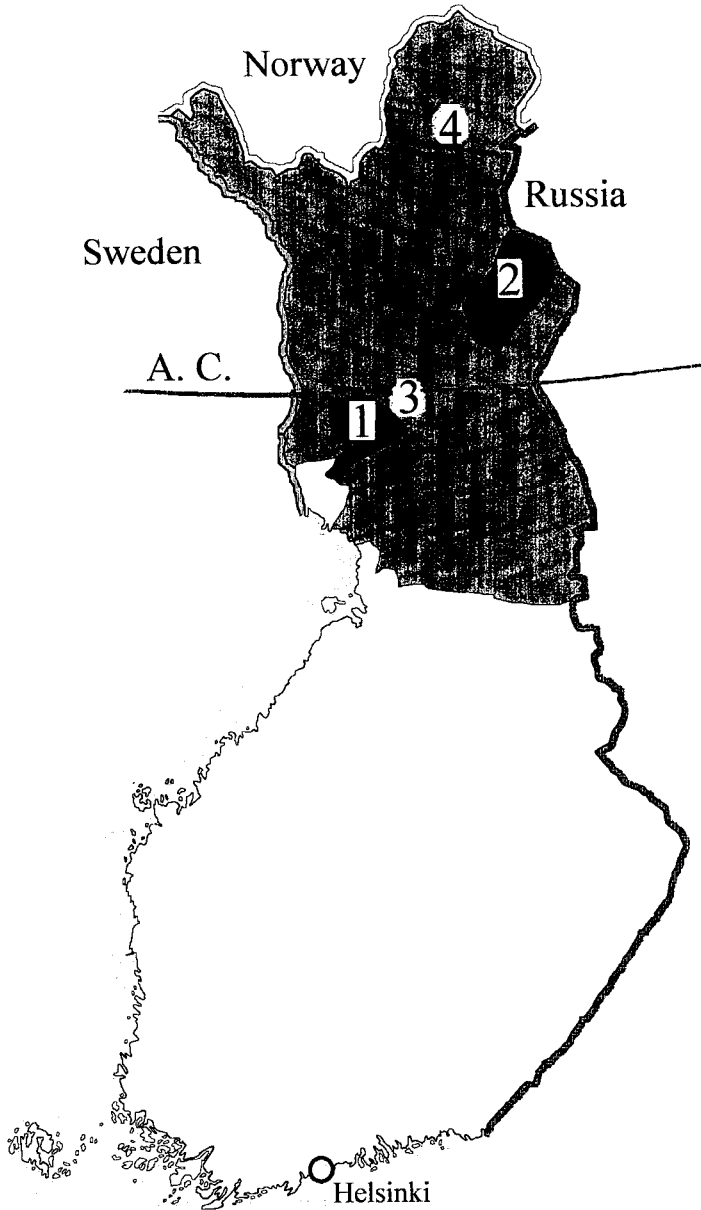


Fig. 1. The Finnish reindeer husbandry area (light shade) and the trial herding co-operatives (dark shade): 1, Palojärvi herding co-operative (PJ); 2, Kemin-Sompio herding co-operative (K-S); 3, Rovaniemi Meteorological Station; 4, Kaamanen Experimental Reindeer Herd; A.C., Arctic Circle.

dependent variable, (ivermectin treatment) *Group* as independent variable, and *Starting weight*, *Sex*, *Herding co-operative*, and *Time* (days to slaughter from 1 October, 1995), as covariates.

3. Results

The treatments were easily performed as planned and no adverse reaction was observed in any animal. The amounts of calves registered as those selected as replacements were very similar: 8 of 177 (4.5%) in Group 1, 9 of 177 (5.1%) in Group 2, and 9 of 175 (5.2%) in Group 3. Twenty-one of these 26 replacements (85%) were females. On average, the starting weight at the treatment date of the replacements was slightly higher than that of the others, females: 18.4 (SD 3.4) compared to 17.0 kg (3.5) ($P=0.08$, t test), and males: 19.6 (3.1) compared to 17.9 kg (3.7) ($P=0.3$). The proportion of missing calves did not differ between groups, and was 48.6% (86) for Group 1, 52.0% (92) for Group 2, and 53.7% (94) for Group 3 ($P=0.62$, χ^2 test). The missing calves had non-significantly lower starting weights than the others; the mean starting weight was 17.3 kg (3.5) for those missing and 17.8 kg (3.7) for those known to have been slaughtered or selected to live ($P=0.15$). There was no difference in the proportion of females (141 of 273, 51.6%) missing compared with that of males (131 of 256, 51.2%).

Both starting weights and carcass weights differed between the two herding co-operatives (Table 1). Mean carcass weights of the treatment groups were similar (Table 2). Regression coefficients of the covariates (*Time*, *Starting weight*, *Sex* and *Herding co-operative*) were significant, except that of the *Herding co-operative*, and are given in Table 3.

In the few hides examined in January, there were only a few warbles. When combining both the ivermectin treated groups, there were 4 treated and 4 control animals, with an median (range) of 3.5 (0 to 6) and 8.5 (4 to 22) warbles, respectively. This difference was nearly significant ($P=0.06$, one-sided Mann–Whitney test).

Table 1

Starting weights (early July body weight) and carcass weights (kg) of reindeer calves from two herding co-operatives in Finland 1995

	Palojärvi		Kemin-Sompio					
	Females <i>n</i> =56	Males <i>n</i> =56	Females <i>n</i> =55	Males <i>n</i> =64				
Starting weight, s.d.	18.4	3.4	20.7	3.6	15.1	2.7	16.6	2.9
Carcass weight, s.d.	20.2	2.6	22.4	3.0	19.0	2.5	20.4	2.6

Table 2

Carcass weights (kg) of reindeer calves from two herding co-operatives in Finland, untreated or treated with ivermectin during the ear marking in early July, 1995

Group	<i>n</i>	Mean	Adjusted mean ^a	SE
1. Untreated	75	20.3	20.6	0.22
2. Ivermectin injection	59	20.7	20.5	0.25
3. Ivermectin topical	62	20.4	20.2	0.24

^aAdjusted for sex, starting weight, time, and herding co-operative.
 $P=0.53$.

Table 3

The regression of covariates for slaughter weight of 196 reindeer calves in the trial of ivermectin treatment (summer 1995, Finland)

Covariate	b	SE (b)	t	P
Time ^a (d)	-0.031	0.006	-5.24	0.000
Starting weight ^b (kg)	0.51	0.04	11.86	0.000
Sex ^c	-0.96	0.29	-3.32	0.001
Herding co-operative ^d	0.59	0.34	1.73	0.085

^a1. October 1995 to day of slaughter.

^bbody weight during treatment.

^c0=male, 1=female.

^d0=PJ, 1=K-S.

4. Discussion

In field trials of this type, the individual animal owners cannot be equally motivated, and therefore the reporting quota will vary between owners. We do not know how many of the missing animals have really been lost, and how many just ignored. According to some herders, at least tens of the calves selected to live or slaughtered privately during minor round-ups are missing from our data. According to official statistics, the calf percentage during the year of trial was 71 for PJ and 77 for K-S (Anon, 1997). Given that some hinds were barren and that some calves died at an early age (before the ear-marking), the total losses between the ear-marking and slaughter in these two co-operatives hardly reached 20%. This indicates that the main cause of the high losses in our trial was probably registration failure. The herding co-operative has common pastures and co-operative herding. As the systematic sampling used to allocate animals was not related to ownership, it is unlikely that the exclusion of some individual owners' animals could have biased the results. Loss of animals was not associated with treatment.

We were aware of the possibility that a relatively high proportion of trial animals would be lost to follow-up. Anyhow, we expected that the 529 calves would probably be enough to meet our original requirement of 375 animals (1.4-fold). The number of animals recorded as slaughtered (= actual sample size) was only 231, giving about 75% power instead of the 90% desired (Altman, 1991). However, the slaughter weights of all the three groups were so similar that the absence of treatment effect is extremely unlikely to have been caused by error alone.

The main result of this work (no effect of treatment on the slaughter weights) was unexpected, given that Oksanen and Nieminen (1995) reported a significant increase in the growth of male reindeer calves following one ivermectin injection during the summer. However, their trial was done with a relatively small number of calves in the Kaamanen Experimental Reindeer Herd, and they did not get any increase in growth of female reindeer calves either. In another trial, repeated treatments with a broad-spectrum benzimidazole anthelmintic resulted in an increase in reindeer calves' live weight gain during summer and autumn (Oksanen et al., 1996). That report, too, was based on a small material in the Kaamanen herd. It is possible that parasite infection pressure in the

Kaamanen herd differs from these commercial co-operatives. In any case, the herd and its range are much smaller in Kaamanen, where the landscape is more open and barren. The population density is higher in Kaamanen: about 7.5 reindeer/km², compared with 2 and 4 in PJ and K-S, respectively (J. Kumpula, pers. comm.).

If the food situation is good, reindeer select the feed items flourishing at any time (Nieminen, 1985), often from shrubs and bushes, where infective parasite larvae probably are scarce. Obviously, antiparasitic treatment can cause benefit only in parasitized animals. Host–parasite interactions are complex, and it could also be assumed that animals on worn and heavily infected pastures would be rapidly reinfected after the persistent effect of the antiparasitic drug has passed. This could decrease the positive treatment effect or even turn it negative in case treatment interferes with the build-up of immunity against parasites.

These two herding co-operatives were a convenience sample out of three volunteers. As seen from the calf percentages, they are more productive than the average co-operative, which can perhaps even be expected from volunteers. So, they are probably not totally representative to all the 56 Finnish herding co-operatives in terms of productivity and level of parasitism. It is known that there are big geographical differences in the amount of warbles in reindeer (Helle, 1980).

Perhaps one factor leading to the lack of effect of the treatments was that the summer 1995 was rather cool and rainy, causing slow development of free-living stages of parasites. This is best recognised regarding oestrid flies. As warble fly pupae need a minimum temperature of 11°C for development, and the lower threshold for adult flies to fly is 14–15°C (optimum 17–27°C) (Breyev, 1961), the mean temperature of 13.0°C in July and 12.4°C in August in Rovaniemi (Fig. 1) (statistics of the Finnish Meteorological Institute) did not favour them. Perhaps, partly therefore, the amount of warbles was low also in the untreated animals. Helle (1980) counted 103 (SD 82) and 25 (20) warbles in the hides of reindeer calves from the K-S co-operative during the winters 1978–9 and 1979–80, respectively. However, his work was done before the winter antiparasitic treatment became common, and lower infection pressure can now be expected. The cool summer may also have shifted the warble fly flight season forward, which reduced the treatment efficacy.

The variables affecting the slaughter weight were not surprising. The positive association of starting weight is as expected, and the lower weight of females and the decrease in weight during the winter have been documented before (Nieminen and Petersson, 1990). Therefore, reindeer herders commonly attempt to get the slaughter done as early as possible, which also saves winter lichen pastures. It is, however, obvious that the regression coefficient in Table 3 is only applicable within the time span of slaughter in this trial, from October, 1995 to January, 1996.

It is perhaps surprising that the regression coefficient is positive for the K-S herding co-operative (Table 3), so clearly higher were the PJ carcass weights than those of K-S (Table 1). The difference, however, was even more pronounced in starting weights.

The nearly significant decrease in the number of warbles indicates that if slaughter for some reason is delayed, better hides could be expected from ivermectin-treated reindeer calves. This would increase the value of slaughter calves, but probably would not alone justify treatment.

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