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# A meta-analysis of the milk-production response after anthelmintic treatment in naturally infected adult dairy cows

Javier Sanchez[a,*], Ian Dohoo[a], Jeromy Carrier[b], Luc DesCôteaux[b]

[a] *Department of Health Management, Atlantic Veterinary College, University of Prince Edward Island,*
*550 University Avenue, Charlottetown, PEI, Canada C1A 4P3*
[b] *Faculté de Médécine Veterinaire, Université de Montreal, Sciences Cliniques,*
*St-Hyacinthe, Que., Canada J2S 7C6*

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## Abstract

Meta-analysis was used to estimate the effects of anthelmintic treatment on milk production in dairy cows. The literature search included peer-reviewed journals (both full articles and abstracts), conference proceedings and theses and included documents written in English, Spanish, French, Portuguese or Italian. The study outcome was defined as the difference in milk production (kg/cow per day) between treated and untreated cows. Random effect meta-analyses were performed on 75 trials published between 1972 and 2002. The combined estimate after controlling for publication bias and/or small-study effect was of 0.35 kg/cow per day. Significant variation among studies was detected and although several variables were associated with the study outcome, they did not significantly reduce the unexplained variability among trials. Trials reporting the use of endectocides had higher milk-production response compared with trials using older anthelmintics. Similarly, whole-herd treatment trials or trials which applied the treatment in mid-lactation or strategically throughout the year had higher response compared with calving or dry-period treatment trials. Trials reporting the results as total 305-day milk production had lower response compared with trials which measured production as daily milk weight. Primiparous cows trials had lower responses compared with multiparous cows trials.

*Keywords:* Anthelmintic treatment; Dairy cattle; Milk production; Meta-analysis; Nematodes

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[*] Corresponding author. Tel.: +1-902-566-0995; fax: +1-902-566-0823.
*E-mail address:* jsanchez@upei.ca (J. Sanchez).

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## 1. Introduction

The milk-production responses obtained from field trials of anthelmintic treatments in adult dairy cows have been equivocal, and consequently, clear guidelines as to when anthelmintic treatments should be applied have not been available. Although adult dairy cows can harbor an important number of gastrointestinal parasites (mainly *O. ostertagi*) (Agneessens et al., 2000; Borgsteede et al., 2000), the lack of accurate diagnostic tests for this group of animals (Gross et al., 1999; Eysker and Ploeger, 2000) makes it difficult to establish a threshold for anthelmintic treatment (Vercruysse and Claerebout, 2001).

To obtain an overall estimate of the effect of deworming adult dairy cattle on milk production, Gross et al. (1999) performed a narrative review of more than 80 trials in dairy cattle and concluded that a median increase in milk production of 0.63 kg/cow per day might be expected after anthelmintic treatment. Although traditional narrative reviews have been used widely in veterinary literature, they are subjective in nature and therefore prone to a reviewer bias (Egger and Davey Smith, 2001). They also do not easily take into account the precision of the treatment response estimates; so, studies tend to be weighted equally.

On the other hand, a meta-analysis allows a reviewer to arrive at conclusions that might be more accurate than those from a non-quantitative, narrative review (Rosenthal and DiMatteo, 2001). A meta-analysis is a systematic review of the literature followed by a quantitative compilation of all relevant results in which the precision of each individual trial is taken into account. A meta-analysis can be biased by the exclusion or inclusion criteria used in the study selection process or by the methods chosen to combine results from the selected studies (Egger and Davey Smith, 2001). However, these biases can be minimized when a detailed protocol specifying the selection of the studies and collection and analysis of the data is followed.

Our objective was to use a meta-analysis to estimate the extent to which anthelmintic treatment (with a variety of drugs and treatment protocols) influenced milk production in dairy cows.

## 2. Material and methods

### 2.1. Literature review

The literature review was based on the following databases: CAB Abstracts (1972–2002) and Medline (1966–2001). The keyword combinations used were “anthelmintic dairy cattle”, “milk production nematodes”, “milk production anthelmintic”, “dairy cows dairy herds anthelmintics”. A total of 416 references related to parasitism in cattle were identified. References were removed if the article pertained to species other than dairy cattle, pertained to the use of anthelmintics in ages other than lactating-age dairy cows, the trial animals were artificially infected, the trial did not measure milk production or if the article was not written in English, Spanish, French, Portuguese or Italian. The search was not restricted to peer-reviewed journals and it included abstracts, conference proceedings and theses. In addition, all the references related to milk-production trials cited in a recent review paper (Gross et al., 1999) were identified. A total of 78 potential articles were identified for the meta-analysis. Bibliographies of retrieved articles were examined for further references.

### *2.2. Outcome evaluated and data extraction*

The mean difference in milk production between treated and control group in kg/cow per day was used as the outcome. If the trial reported this outcome using any other time frame (e.g. actual 305-day milk yield, projected 305-day milk yield) or measurement (e.g. liters, pounds), the outcome was transformed to kg/cow per day.

The precision of the estimate reported was based on the standard errors (S.E.) or standard deviations (S.D.) of the treatment and control groups. If the paper reported separate estimates for each group, they were recorded as such. If the paper reported a common S.E. (or S.D.), that estimate was used for both groups. If the paper only reported a $Z$ statistic or $P$, an estimate of a common S.E. was computed. For papers that only reported a $P$ less than or equal to a given value (e.g. $<0.05$), then that given value was taken and the $P$ and S.E. computed as above. Finally, for studies that simply reported a non-significant effect, $P$ values of 0.15, 0.3 and 0.5 were assigned and compared. The $P$ value that produced the smallest (most conservative) estimate of the overall treatment effect was selected for the calculation of the S.E.

Data only were extracted from clinical trials, although the studies need not have been either randomized or blinded.

The information described in Table 1 also was extracted. All this information was extracted from the articles independently by two investigators using a structured data-collection

Table 1
Additional information extracted from the studies considered in the review of anthelmintic treatment and milk-production response in adult dairy cows

| Variable | Description |
|---|---|
| Trial quality | |
| Publication type | Journal indexed in Index Medicus, journal not indexed, abstracts/paper proceedings |
| Randomization | Whether a method of randomization was reported |
| Treatment blind | Whether blinded treatment measurement was reported |
| Control of confounders | Confounders controlled for in the analysis (i.e. age, farm, season, previous milk production, etc.) |
| Trial design | |
| Publication year | Year when the trial was published |
| Formulation | Whether endectocides (e.g. ivermectin, moxidectin, eprinomectin, dectomectin) were used |
| Time of treatment | Dry off: calving, mid-lactation (between 0 and 200 day in milk) or strategic |
| Individual treatment | Whether the treatment was not applied to the whole herd at once |
| Milk length | Period of time (days) milk production was measured |
| Milk measure | Milk production measure (daily weight, 305 actual, 305 projected, etc.) |
| Location | Country where the trial was carried out |
| Parity | Primiparous, multiparous, all combined |
| Pasture exposure | Whether the cows were on pasture-year-round, pasture-seasonal or partially confined |

form. The two datasets were then compared and all the disagreements were resolved by the senior author (Sanchez) re-reviewing the source paper.

## 2.3. *Meta-analyses*

Fixed and random-effects meta-analyses were carried out to evaluate the effect of anthelmintic treatment on milk production. The results from the random-effects meta-analysis are presented in this paper. A random-effects meta-analysis assumes that there is a normal distribution of the study effects and the variance of the distribution is estimated from the data. The method of DerSimonian and Laird (Deeks et al., 2001) was used to estimate the variance for the random-effects model. The heterogeneity statistic $Q$ (Deeks et al., 2001) was used to determine if there was significant variability between studies. Under the null hypothesis of a common treatment effect among trials, this $Q$ statistic follows a chi-squared distribution with $K-1$ degrees of freedom, where $K$ is the number of trials. Because a significant $P$ (i.e. $<0.05$) for the $Q$ statistic was observed, the results from the random-effects model are presented in this manuscript.

Because several biases might influence the results of a meta-analysis, the following procedures were performed to detect (and if needed, to correct for) possible publication bias or other small-study effects. First, the Begg's (Begg and Mazumdar, 1994) and Egger's (Egger et al., 1997) tests were used in combination with a funnel plot (Sterne et al., 2001). If there was any evidence of publication bias from either of these tests or the funnel plot, the "trim and fill" method suggested by Duval and Tweedy (2000) was used to estimate and correct for this publication bias. This method works by omitting studies with large S.E. or low statistical significance (e.g. "small study") until the funnel plot is symmetrical. Then, using the trimmed funnel, the center of the plot is estimated and the omitted studies are put back in along with their hypothetical "missing counterparts" around the center (Sterne et al., 2001).

## 2.4. *Meta-regression*

### 2.4.1. *Trial quality characteristics*

To investigate factors which might have influenced trial results, weighted regression analyses (meta-regression) between the trial effect and trial quality characteristics (including precision of estimate) were performed. This was done in two steps. First, an unconditional analyses were carried out between the trial outcome and trial precision, randomization, blinding, control for confounders in the analysis and publication type. Subsequently, all unconditionally significant variables ($P \leq 0.15$) were retained and evaluated in a multivariable analysis.

## 2.5. *Other trial characteristics*

Meta-regression analyses also were used to evaluate the effects on the study outcome of: product formulation (endectocides or other drugs), parity of cows (primiparous, multiparous or all combined), time of treatment (dry off, calving, mid-lactation or strategic treatment), trial length (days after treatment for which milk production was measured), individual treatment (versus whole-herd treatment), country where the trial was performed and pasture exposure.

### 2.6. Cumulative meta-analysis

A random-effects cumulative meta-analysis was performed using the 75 trials. This methodology computed an overall estimate of treatment effect at the time each trial was published. A cumulative meta-analysis may be used to identify (retrospectively) when a treatment effect reached conventional levels of statistical significance. However, we used the method to identify possible temporal patterns in the trial results.

The between-trial variance was obtained using the moment estimator of the variance (Thompson and Sharp, 1999) and no adjustment for clustering of results within author was carried out, because the number of trials per author was low. All analyses were carried out using the statistical program Stata, Version 8 (Stata Corp, 2001).

## 3. Results

### 3.1. Literature review

Of the 78 articles identified by the literature review, 7 of them could not be retrieved (6 English and 1 Italian). Of the remaining 71, 7 articles were not used in the analyses for the following reasons: 4 were review articles with no original data (Todd et al., 1975; Fox, 1979; Wilkinson, 1992; Gasbarre and Stout, 1998), 2 were duplicates (Fisher, 1980; McPherson et al., 1999), and 1 only evaluated the effects of flukes on milk production (Froyd, 1973).

The remaining 64 articles described 97 anthelmintic trials. Out of these, 8 articles (9 trials) did not contain data on the trial outcome (Moore et al., 1974; Beatty et al., 1975; McQueen et al., 1977; Alvarez et al., 1977; Bell, 1980; Glenn et al., 1982; Kloosterman and Albers, 1982; Prosl et al., 1983). From the 9 trials that did not report the outcome of interest, 6 reported a non-significant effect of treatment on milk production while the other 3 did not report any value. A further 11 articles (13 trials presented in Table 2 and listed in the references) presented data in a manner that was not usable in the meta-analyses (usually no estimate of the precision of the results was available). Out of the 13 trials not usable in the meta-analysis, 3 did not report the length of the milk production measurement so the outcome could not be computed, 1 reported a negative effect and 9 reported a positive effect of treatment on milk production (2 were significant, 7 did not report the significance). These 13 trials used, on average, 241 cows and ranged from 20 to 1643 animals. Of the 19 articles identified above as containing at least some trial results which were not usable, three also reported some trial results that were usable in the meta-analysis. Consequently, a total of 48 articles with results from 75 trials were used for the meta-analysis (articles presented in Table 3 and listed in the references). Forty-five of these articles were written in English, two were in French and one was in Spanish. Summaries of the main trial characteristics of the trials not usable and used in the meta-analysis are presented in Tables 2 and 3, respectively.

Out of the 75 trials used in the meta-analysis, 16 reported a negative effect and the other 59 reported a positive response (Table 4).

Table 2
Summary of the 13 trials not usable in the meta-analysis

| Reference | Drug | Parity | Number of cows | Control conf.[a] | Milk measure[b] | Mean difference | Significance[c] | Reason not used[d] |
|---|---|---|---|---|---|---|---|---|
| Brown and Maniscalco (1974) | Coumaphos | 2nd+ | 36 | No | DW | $-0.54$ | NR | A |
| Harris and Wilcox (1976) | Coumaphos | 2nd+ | 85 | Yes | NR | – | NS | B |
| Todd et al. (1978) | Coumaphos | 2nd+ | 175 | No | 305 | 1.14 | NR | A |
| Todd et al. (1978) | Coumaphos | 2nd+ | 157 | No | 305 | 0.11 | NR | A |
| Pouplard (1978) | Thiabendazole | 2nd+ | 190 | No | 305 | 1.31 | NR | A |
| Pouplard (1978) | Thiabendazole | 1st | 47 | No | 305 | 3.52 | NR | A |
| McBeath et al. (1979) | Fenbendazole | All | 174 | Yes | 305 | 0.57 | NR | A |
| Corba et al. (1980) | Thiabendazole | 2nd+ | 84 | No | 305 | 0.92 | NR | A |
| Gremillet (1981) | Thiabendazole | All | 46 | No | NR | – | NR | B |
| Kloosterman and Albers (1982) | NR | 2nd+ | NR | Yes | 305 | 0.67 | S | C |
| Mathews et al. (1983) | Fenbendazole | 2nd+ | NR | Yes | 140 | 1.10 | S | C |
| Thomas et al. (1984) | Fenbendazole | NR | 1643 | Yes | NR | – | NS | B |
| Yazwinski et al. (1999) | Moxidectin | NR | 20 | No | DW | 0.36 | NR | A |

[a] Control for confounding (e.g. previous lactation, age, season, farm) in the analysis.

[b] DW = daily weight, 305 = 305-day total milk production (actual or projected), NR = not reported.

[c] Statistical significance reported: NR = not reported, NS = not significant, S = significant ($P \leq 0.05$).

[d] Reason not being used: (A) no precision or $P$-value reported, (B) no measure of milk production reported; (C) no sample size reported.

Table 3
Summary of the 75 trials used in the meta-analysis

| Trial ID | Reference | Drug | Parity | Number of cows | Control conf.[a] | Milk measure[b] | Mean benefit | Significance[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | Todd et al. (1972) | Copper sulfate | 2nd+ | 692 | No | DW | 0.94 | <0.01 |
| 2 | Todd et al. (1972) | Phenotiazine | 2nd+ | 427 | No | DW | 1.10 | <0.01 |
| 3 | Todd et al. (1972) | Thiabendazole | 2nd+ | 397 | No | DW | 1.02 | <0.01 |
| 4 | Bliss and Todd (1973) | Coumaphos | 2nd+ | 1003 | No | DW | 0.54 | <0.01 |
| 5 | Bliss and Todd (1974) | Thiabendazole | 2nd+ | 488 | Yes | 305 | 0.63 | <0.1 |
| 6 | Bliss and Todd (1976) | Thiabendazole | 2nd+ | 267 | Yes | 305 | 0.79 | <0.05 |
| 7 | Harris and Wilcox (1976) | Thiabendazole | 2nd+ | 315 | Yes | 305 | −0.93 | NS |
| 8 | McQueen et al. (1977) | Levamisole | 2nd+ | 48 | Yes | 220 | 1.12 | <0.05 |
| 9 | McQueen et al. (1977) | Levamisole | 2nd+ | 48 | Yes | 220 | 0.75 | <0.05 |
| 10 | McQueen et al. (1977) | Levamisole | 2nd+ | 48 | Yes | 220 | 1.23 | <0.05 |
| 11 | van Adrichem and Shaw (1977) | Cambendazole | 1st | 48 | No | 287 | 0.67 | <0.05 |
| 12 | Barger (1979) | Fenbendazole | 2nd+ | 335 | No | DW | −0.25 | NS |
| 13 | Pluimers (1979) | Thiabendazole | 2nd+ | 542 | Yes | 305 | 0.75 | <0.01 |
| 14 | Gibbs (1980) | Thiabendazole | 2nd+ | 212 | No | 305 | −0.61 | NS |
| 15 | Heider et al. (1980) | Thiabendazole | 2nd+ | 84 | No | 305 | 0.43 | NS |
| 16 | Heider et al. (1980) | Thiabendazole | 1st | 28 | No | 305 | 0.05 | NS |
| 17 | Wilk et al. (1980) | Thiabendazole | All | 1180 | Yes | 305 | 0.31 | <0.01 |
| 18 | Wilk et al. (1980) | Thiabendazole | All | 1520 | Yes | 305 | 0.44 | <0.01 |
| 19 | Frechette and Lamothe (1981) | Morantel | 2nd+ | 217 | Yes | 305 | 0.84 | <0.05 |
| 20 | Morhain and Legrand (1981) | Thiabendazole | 2nd+ | 12 | Yes | DW | 0.71 | NS |
| 21 | Morhain and Legrand (1981) | Thiabendazole | 2nd+ | 12 | Yes | DW | −0.26 | NS |
| 22 | Thomas et al. (1981) | Thiabendazole | 2nd+ | 96 | Yes | 305 | −0.53 | NS |
| 23 | Barger and Lisle (1982) | Fenbendazole | 2nd+ | 316 | Yes | 305 | −0.14 | NS |
| 24 | Bliss et al. (1982) | Morantel | 2nd+ | 210 | Yes | 305 | 1.23 | <0.05 |
| 25 | Fisher and MacNeill (1982) | Levamisole | All | 116 | Yes | 305 | −0.36 | NS |
| 26 | Fisher and MacNeill (1982) | Levamisole | All | 42 | Yes | 305 | 3.16 | <0.05 |
| 27 | Michel et al. (1982) | Levamisole | All | 3660 | Yes | 305 | 0.19 | NS |
| 28 | Michel et al. (1982) | Thiabendazole | All | 3660 | Yes | 305 | 0.17 | NS |
| 29 | Michel et al. (1982) | Fenbendazole | All | 3660 | Yes | 305 | 0.21 | NS |

Table 3 (*Continued*)

| Trial ID | Reference | Drug | Parity | Number of cows | Control conf.[a] | Milk measure[b] | Mean benefit | Significance[c] |
|---|---|---|---|---|---|---|---|---|
| 30 | Fox and Jacobs (1984) | Levamisole | 2nd+ | 343 | Yes | 305 | 0.05 | NS |
| 31 | Gouffe et al. (1984) | Albendazole | All | 341 | Yes | DW | 1.10 | $<0.05$ |
| 32 | Fetrow et al. (1985) | Thiabendazole | 1st | 218 | Yes | 305 | 0.83 | NS |
| 33 | Fetrow et al. (1985) | Thiabendazole | 2nd+ | 486 | Yes | 305 | −0.34 | 0.73 |
| 34 | Block and Gadbois (1986) | Morantel | 2nd+ | 2660 | Yes | DW | 1.20 | $<0.05$ |
| 35 | Miller et al. (1986) | Coumaphos | 1st | 80 | Yes | 305 | −0.26 | $>0.05$ |
| 36 | Miller et al. (1986) | Thiabendazole | 1st | 25 | Yes | 305 | −2.17 | $>0.05$ |
| 37 | Miller et al. (1986) | Thiabendazole | 1st | 30 | Yes | 305 | 1.38 | $>0.05$ |
| 38 | Miller et al. (1986) | Coumaphos | 2nd+ | 242 | Yes | 305 | 0.88 | $>0.05$ |
| 39 | Miller et al. (1986) | Thiabendazole | 2nd+ | 78 | Yes | 305 | −0.31 | $>0.05$ |
| 40 | Miller et al. (1986) | Thiabendazole | 2nd+ | 57 | Yes | 305 | 0.43 | $>0.05$ |
| 41 | O’Farrell et al. (1986) | Febantel | All | 807 | Yes | 305 | 0.32 | $<0.05$ |
| 42 | Sommefeldt (1986) | Thiabendazole | 1st | 68 | No | DW | −1.10 | $>0.05$ |
| 43 | Takagi and Block (1986) | Coumaphos | 2nd+ | 28 | No | DW | 1.02 | $<0.09$ |
| 44 | Bisset et al. (1987) | Oxfendazole | 2nd+ | 4500 | Yes | 251 | 0.21 | $<0.01$ |
| 45 | Block et al. (1987) | Levamisole | 2nd+ | 1296 | No | DW | 1.24 | $<0.05$ |
| 46 | Biondani and Steffan (1988) | Fenbendazole | 2nd+ | 530 | No | 305 | 0.66 | $<0.05$ |
| 47 | Ploeger et al. (1989) | Ivermectin | 2nd+ | 469 | Yes | 305 | 0.67 | $<0.01$ |
| 48 | Tharaldsen and Helle (1989) | Fenbendazole | 1st | 184 | Yes | 305 | −0.32 | $>0.05$ |
| 49 | Tharaldsen and Helle (1989) | Fenbendazole | 2nd+ | 232 | Yes | 305 | −0.72 | $<0.05$ |
| 50 | De Rond et al. (1990) | Ivermectin | 2nd+ | 20 | Yes | 133 | 0.84 | $<0.10$ |
| 51 | De Rond et al. (1990) | Febantel | 2nd+ | 20 | Yes | 133 | 0.89 | $<0.05$ |
| 52 | Ploeger et al. (1990b) | Albendazole | 1st | 347 | Yes | 305 | 0.64 | $<0.01$ |
| 53 | Ploeger et al. (1990a) | Albendazole | 2nd+ | 1385 | Yes | 305 | 0.44 | $<0.01$ |
| 54 | Sanyal et al. (1992) | Fenbendazole | 2nd+ | 96 | Yes | DW | 1.42 | 0.02 |
| 55 | Spence et al. (1992) | Fenbendazole | 2nd+ | 779 | Yes | DW | 0.60 | $<0.05$ |
| 56 | Bhongade et al. (1993) | Albendazole | 2nd+ | 50 | Yes | DW | 0.65 | $<0.05$ |
| 57 | Bhongade et al. (1993) | Albendazole | 2nd+ | 50 | Yes | DW | 0.71 | $<0.05$ |
| 58 | Bhongade et al. (1993) | Albendazole | 2nd+ | 50 | Yes | DW | 0.66 | $<0.05$ |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 59 | Bhongade et al. (1993) | Albendazole | 2nd+ | 50 | Yes | DW | 0.67 | <0.05 |
| 60 | Sanyal et al. (1995) | Fenbendazole | 2nd+ | 47 | No | DW | 1.96 | <0.05 |
| 61 | Walsh et al. (1995) | Ivermectin | 2nd+ | 498 | Yes | 100 | 0.74 | <0.01 |
| 62 | Kloosterman et al. (1996) | Ivermectin | 1st | 116 | Yes | 305 | 0.41 | 0.38 |
| 63 | Kloosterman et al. (1996) | Ivermectin | 2nd+ | 262 | Yes | 305 | 0.49 | 0.08 |
| 64 | Spence et al. (1996) | Oxfendazole | 2nd+ | 460 | Yes | DW | 0.50 | <0.05 |
| 65 | Murphy (1998) | Moxidectin | All | 137 | No | 140 | 0.75 | NS |
| 66 | Murphy (1998) | Moxidectin | All | 325 | No | 320 | 0.53 | <0.01 |
| 67 | Murphy (1998) | Moxidectin | All | 200 | No | 125 | 0.37 | 0.08 |
| 68 | Carrier et al. (1999) | Eprinomectin | 1st | 61 | Yes | 305 | 0.83 | NS |
| 69 | Carrier et al. (1999) | Eprinomectin | 2nd+ | 229 | Yes | 305 | −0.24 | NS |
| 70 | DesCoteaux et al. (2001) | Ivermectin | 1st | 67 | Yes | 305 | 1.14 | <0.05 |
| 71 | McPherson et al. (2001) | Eprinomectin | 1st | 182 | Yes | DW | −0.10 | 0.78 |
| 72 | McPherson et al. (2001) | Eprinomectin | 2nd+ | 560 | Yes | DW | 0.60 | 0.005 |
| 73 | Pfister et al. (2001) | Eprinomectin | 2nd+ | 490 | No | 305 | 2.14 | <0.001 |
| 74 | Pfister et al. (2001) | Trichlorfon | 2nd+ | 385 | No | 305 | 1.88 | <0.001 |
| 75 | Nødtvedt et al. (2002b) | Eprinomectin | All | 901 | Yes | DW | 0.94 | 0.002 |

[a] Control for confounding (i.e. previous lactation, age, season, farm) in the analysis.

[b] DW = daily weight, 305 = 305 total milk production (actual or projected).

[c] Statistical significance reported: NS = not significant (if actual *P* value not reported a value of 0.15 was assumed).

Table 4
Descriptions of the trial effect (mean difference kg/cow per day), sample size and number of trials used in the meta-analysis of anthelmintic treatment of naturally infected lactating dairy cows

| Significance | Percentile | | Total sample size | Number of trials |
|---|---|---|---|---|
| | 25th | 75th | | |
| ≤0.05 | | | | |
| Benefit | 0.62 | 1.13 | 23852 | 40 |
| Disadvantage | −0.72 | −0.72 | 232 | 1 |
| >0.05 | | | | |
| Benefit | 0.21 | 0.83 | 13306 | 19 |
| Disadvantage | −0.61 | −0.25 | 2734 | 15 |

### 3.2. *Meta-analysis methods*

The sensitivity analysis using *P* values of 0.15, 0.3 and 0.5 produced overall treatment-effect estimates of 0.46, 0.47 and 0.49 kg/cow per day, respectively. Based on these results, the value of 0.15 was selected as the *P* value for studies which only reported results as “non-significant”. The DerSimonian and Laird pooled estimate of the mean difference in milk production was 0.46 kg/cow per day (95% CI 0.36, 0.56). A forest plot presenting the results from each trial and the combined effect is shown in Fig. 1. The statistical approaches for the detection of publication bias or small-study effect showed differing results. Although the Begg’s test reported a non-significant bias ($P = 0.73$), the Egger’s test reported a highly significant value ($P < 0.001$)—and a visual inspection of the funnel plot (Fig. 2) suggested that publication bias might have been present. This plot is based on the fact that the precision of the treatment effect will increase as the sample size (e.g. number of cows) increases. Treatment effects from small studies will therefore scatter more widely at right end of the graph. In the absence of bias, the plot will resemble a symmetrical funnel (Sterne et al., 2001). If publication bias is present, few studies with small (or absent) treatment effects and large standard errors will be present, resulting in a gap in the lower right quadrant of the graph. The random-effects “trim-and-fill” method reduced the combined pooled estimate from 0.46 to 0.35 (95% CI 0.25, 0.45). This method also indicated that an additional 12 trials (small square boxes in Fig. 2) would have been necessary to remove this apparent publication bias (or other small-study effects).

Only 11 trials reported both a formal randomization procedure and blinding. The pooled estimate based only on these 11 trials (0.33) was similar to that reported by the “trim-and-fill” method suggesting a possible association between trial quality and effect estimate.

### 3.3. *Meta-regression analyses*

Table 5 shows the results obtained from the meta-regression analyses of the associations between trial effect and trial quality characteristics. Both the unconditional and multivariable analyses showed an association between trial effect and precision (as would have been expected based on the previous assessment of publication bias). Similarly, the trial outcome was associated with publication type and control for confounders. If control for other

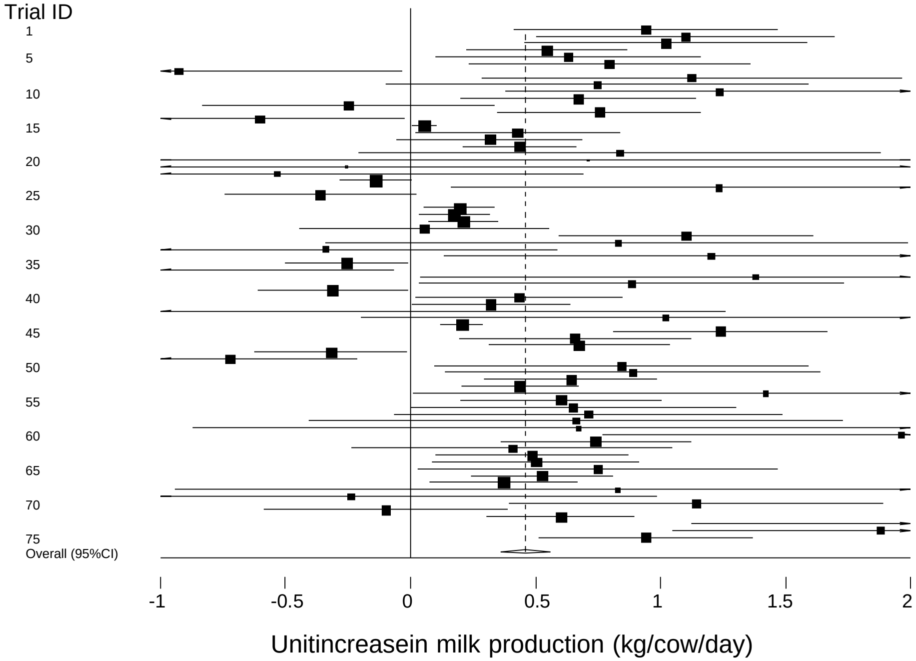

Fig. 1. Forest plot of the effects of anthelmintic treatment on milk-production response in lactating dairy cows (kg/cow per day). The overall estimate was derived from the random-effect meta-analysis. Lines with arrows are truncated; length of the horizontal lines indicate 95% CIs of the effect estimate. The center of square represents the point estimate and the area of the square is proportional to the weight assigned to the trial. Dotted line represents the overall estimate obtained from the random-effect meta-analysis. The < > at the bottom of the dashed line shows the confidence interval for the overall effect. The solid vertical line marks the value where anthelmintic treatment would have no effect. Trial ID refers to values shown in Table 3.

Table 5
Meta-regression analysis of the precision and two measures of methodological quality on the trial effect ($n = 75$)

| Factor | Effect on overall estimate | | |
|---|---|---|---|
| | *b* | 95% CI | *P* |
| Unit increase in standard error | 0.86 | 0.28, 1.44 | 0.003 |
| Control confounding | | | |
| No ($n = 19$) | Baseline | | |
| Yes ($n = 56$) | −0.25 | −0.51, 0.01 | 0.06 |
| Referenced in Index Medicus | | | 0.03 |
| Indexed ($n = 36$) | Baseline | | |
| Not indexed ($n = 13$) | 0.23 | −0.005, 0.47 | 0.06 |
| Abstracts/conference proceedings ($n = 26$) | −0.13 | −0.44, 0.18 | 0.42 |

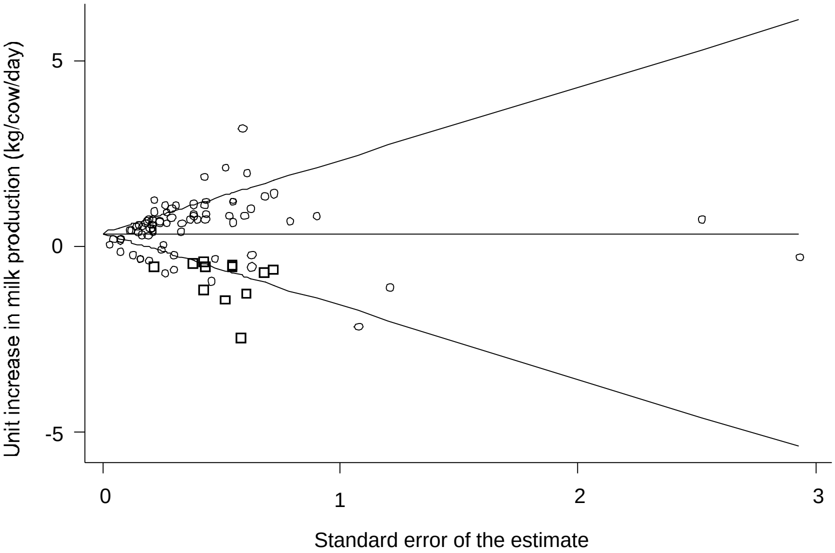

Fig. 2. Funnel plot of the point estimates of the effect of anthelmintic treatment on milk-production response (kg/cow per day). Square points were hypothetical studies added by the "trim and fill" procedure to correct for publication bias or small-study effect.

confounders was used in the statistical analysis, the mean difference in milk production was approximately 0.25 kg/cow per day lower than in trials that did not control for confounders in the analysis. Correlations among trial quality characteristics were evaluated to determine if collinearity was a problem in the multivariable analysis. The highest correlation between these predictor variables was 0.52 between control for confounders and publication in non-indexed journals—suggesting that collinearity was not affecting the regression coefficients.

The results from the meta-regression analyses performed between the trial outcome and variables reflecting other trial characteristics are presented in Table 6. Although the variables evaluated in this analysis did not substantially reduce the variance between studies, four of them (time of treatment, individual treatment, trial length and milk measure) were significantly associated with the trial effect. For example, studies that applied the anthelmintic treatment to mid-lactation cows or strategically throughout the year had an average response that was approximately +0.4 kg/cow per day higher than trials where the cows were treated either during the dry period or at calving. On the other hand, trials in which individuals were assigned to treatment groups (versus whole-herd treatment) had a substantially lower production response. These two trial characteristics were highly correlated: studies in which individuals were treated generally applied the treatment at the time of calving but whole-herd treatment encompassed all stages of lactation.

In relation to geographic location, trials were categorized as northern and southern: Northern trials were those carried out in Canada, Northern Unites States, north-west Europe. Southern trials were those carried out in southern United States, New Zealand, Australia, Argentina, India and Sri Lanka. Northern trials tended to have higher milk response compared

Table 6
Unconditional meta-regression analyses based on 75 trials of anthelmintic treatment in lactating dairy cattle. Table presents coefficients, standard errors, $P$ and the moment estimator of the between-trail variance, $\tau$ ($n = 75$))

| Factor | $b$ | 95% CI | $P$ | $\tau$ |
|---|---|---|---|---|
| Null model ($n = 75$)[a] | 0.46 | 0.36, 0.56 | <0.001 | 0.10 |
| Anthelmintic | | | 0.08 | 0.09 |
| Other ($n = 60$) | Baseline | | | |
| Endectocides ($n = 15$) | 0.21 | −0.02, 0.44 | | |
| Time of treatment | | | <0.001 | 0.09 |
| Dry off/calving ($n = 42$) | Baseline | | – | – |
| Mid-lactation ($n = 15$) | 0.44 | 0.17, 0.71 | 0.001 | – |
| Strategic ($n = 18$) | 0.40 | 0.14, 0.65 | 0.002 | – |
| Level of treatment | | | <0.001 | 0.09 |
| Whole herd ($n = 32$) | Baseline | | | |
| Individual cows ($n = 43$) | −0.40 | −0.61, −0.20 | | |
| Milk length ($n = 75$) | −0.002 | −0.002, −0.001 | 0.002 | 0.08 |
| Milk measure | | | <0.001 | 0.08 |
| Daily weight ($n = 23$) | Baseline | | – | – |
| 305-Day actual or projected ($n = 41$) | −0.44 | −0.66, −0.21 | <0.001 | – |
| Other (e.g. 100 days total) ($n = 11$) | −0.10 | −0.40, 0.21 | 0.530 | – |
| Parity | | | 0.13 | 0.12 |
| Multiparous ($n = 49$) | Baseline | | – | – |
| Primiparous ($n = 13$) | −0.31 | −0.61, −0.01 | 0.04 | – |
| All combined ($n = 13$) | −0.08 | −0.34, 0.17 | 0.52 | – |

[a] Model containing only the intercept.

with southern trials, but this difference was not significant. Pasture exposure was classified as pasture-seasonal and pasture-year-round. Only 59 trials reported information on pasture exposure (36 were pasture-seasonal and the remaining 23 were pasture-year-round). No statistically significant difference was found between level of pasture exposure and the trial outcome ($b = 0.11$, $P = 0.40$).

### 3.4. Cumulative meta-analyses

The cumulative meta-analysis showed a significant effect after the first trial used in this analysis. However, a pronounced pattern was observed through time (Fig. 3). During the 1970s the trials had the highest treatment response. This estimate tended to decline during the 1980s and start increasing again during the 1990s but without reaching the values observed initially. Control for confounders (and especially controlling for farm effect) was related to publication year; studies carried out during the 1970s were less likely to control for farm effect, so larger responses with significant effects were more likely to be reported (data not shown). Moreover, the type of drug used was related to the publication year. Older drugs (e.g. thiabendazole, morantel, levamisol) were more likely to be used during the 1970s, newer benzimidazole drugs during the 1980s and trials using endectocides (e.g. ivermectin) during the 1990s.

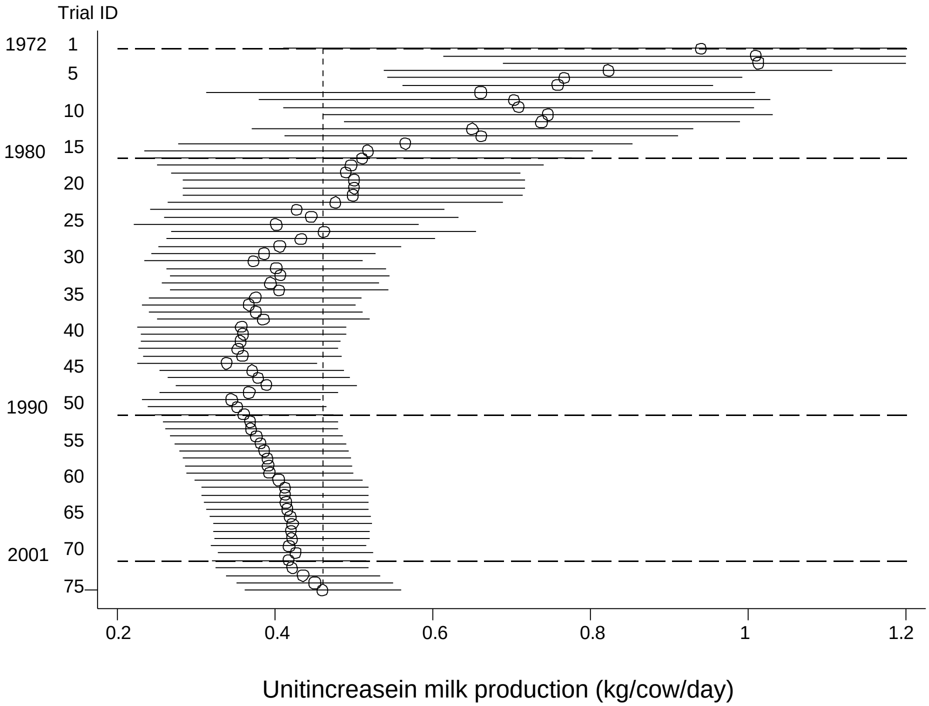

Fig. 3. Cumulative random effect meta-analysis of 75 trials of the effect on milk-production response after anthelmintic treatment in naturally infected lactating dairy cows. The length of the line represent the 95% confidence interval for overall effect based on all preceding studies. The center (circle) on each line marks the point estimate at the time of trial's publication. The dashed vertical line marks the current overall effect estimate (not adjusted for publication bias).

## 4. Discussion

The combined unadjusted and adjusted estimates of 0.46 and 0.35 kg/cow per day, respectively, obtained from the 75 studies were smaller than the 0.63 reported by Gross et al. (1999). However, this estimate is an average effect of the milk-production response from the 75 trials. One of the factors influencing the magnitude of the treatment response will be the level of GIN infection at the farm—which might explain the large variation in treatment response observed between trials (range of −2.17 to 3.16; Table 3).

Although not all the studies used in the review by Gross et al. (1999) were used in the present meta-analysis, a similar median increase in milk production was obtained in this study (Table 4) which suggests some similarity between these two reviews. Only 57 trials used in this meta-analysis matched with those evaluated by Gross et al. ($n = 87$). They had a median increase in milk production of 0.54 kg/cow per day (data not shown; the other 30 studies did not have data suitable for the meta-analyses, did not meet the inclusion criteria or were not retrieved). Using the same 57 studies, the combined estimate derived from the random-effects model after correcting for a possible publication bias was 0.32 (95% CI 0.21, 0.43)—similar to that from our full dataset.

The significant heterogeneity found in this analysis was expected because the differences in trial designs, GIN burdens, treatment protocols, drugs, geographic locations and age groups would have influenced the treatment response.

The visual assessment of publication bias based on the funnel plot (Fig. 2) as well as the results from the Egger's test indicated a publication bias in this analysis. Funnel-plot asymmetries also have been related to inclusion of trials of lower quality (e.g. studies which are not double blind, studies with inadequate allocation of animals to the treatment group) (Sterne et al., 2001). Lower quality trials have also been reported to overestimate the true treatment effect (Moher et al., 1998).

When variables accounting for trial quality were evaluated, three of them were associated with treatment effect and they showed similar trends to those reported by Moher et al. (1998). Two variables not significantly associated with treatment effect were the use of a formal randomization procedure and blinding of treatment measurement. Although studies reporting blinding tended to have a lower effect, those reporting a formal randomized procedure had a higher response—which we had not expected. However, Thompson and Higgins (2002) pointed out that the results obtained from the meta-regression analysis should be interpreted with some caution, especially when the trial characteristics have low variability across studies (which was the case of the present meta-analysis), because the regression analysis can be biased by unmeasured confounders. On the other hand, trials published in indexed journals (e.g. Index Medicus) or trials that used better statistical methodologies (which might reflect the quality of the published study) were associated with lower production response. These analyses suggested that the overall estimate of 0.35 kg/cow per day would be less biased and so more appropriate to report as the overall combined estimate.

Considering the meta-regression analyses of trial design characteristics, trials using macrocyclic lactone endectocides (e.g. ivermectin, moxidectin and eprinomectin) had a higher milk response compared with those using either benzimidazoles or older anthelmintics (i.e. coumaphos, thiabendazole). In contrast, Gross et al. (1999) found the same median increase between new and old anthelmintics. In theory, the new generation of anthelmintic is more effective (especially against immature stages, including larval stages of *O. ostertagi*) (Eysker and Eilers, 1995; Eysker, 1997; Eddi et al., 1997), so a higher response might be expected.

Trials that treated animals either in mid-lactation or strategically (several times during the year) had higher response compared with trials treating animals during the dry-off period or around calving. Gross et al. (1999) found a similar effect (animals treated in mid-lactation had twice as large a production response compared with those treated during the dry period or around calving). Production responses from whole-herd treatment schemes were used in studies in which treatment was given mid-lactation or strategically throughout the year. The larger production response in whole-herd treatment trials might be related to the elimination of the parasites at one point with a more pronounced decrease in the pasture contamination (and consequently, less re-exposure to parasites) or to more frequent treatments (strategic anthelmintic treatment). On the other hand, a larger treatment response might have been expected from cows treated at calving (shortly before their period of highest milk production and physiologic demands). Clarification of this point will require further research.

Production response declined by 2 g for each additional day in the trial follow-up period. Similarly, when the outcome was reported as either 305-actual or 305-projected milk production, the response was lower compared with daily weight trials that reported effect on a per-day basis. Daily weight trials tended to measure milk production for shorter time (median = 95 days) compared with 305 days for whole-lactation trials.

Primiparous cow trials had a lower response than multiparous cow trials. This might reflect different susceptibilities to gastrointestinal parasites between these implicit age groups or the higher production capacity of older cows. Agneessens et al. (2000) found higher worm counts in cows <3 years and those >10 years; Nødtvedt et al. (2002a) reported that first lactation animals had higher fecal egg counts compared with cows in other lactations. On the other hand, Sanchez et al. (2002) found that first lactation animals had lower optical densities from a crude indirect ELISA compared with older animals; this suggests that first lactation animals might be more susceptible to gastrointestinal nematodes. It also has been observed that high-producing animals are more susceptible to GIN—which might suggests a higher treatment response in the high producing group (Hoste et al., 2002).

The distinct pattern observed in the cumulative meta-analysis (Fig. 3) might be related to the combined effect of improvement in study design (including statistical analysis) and/or changes in efficacy of the anthelmintic used. The decline in the effect from 1972 to 1985 might have been due to the use of better trial designs and analytic methods. Although controlling for a farm effect will have a bigger impact on the precision of the estimate, trials which controlled for a farm effect also tended to control for other variables in the analysis. Controlling for confounders was associated with lower milk response (Table 5). The increased response through the 1990s might reflect the greater efficacy of the endectocides. However, this effect might be confounded with the improvement in farm management practices and increasing productivity of cows over the years.

## 5. Conclusion

Our meta-analysis showed that, on average, an increase of milk production of ∼0.35 kg/cow per day might be expected after anthelmintic treatment of naturally infected lactating dairy cows. However, substantial between-trial variation was observed. While this was, in part, due to differences in study design, it also emphasizes the need to have a reliable diagnostic test to identify cow/herds showing the detrimental effects of GIN parasitism to establish a more rational anthelmintic-control program. There was evidence of publication bias (i.e. "small-study effect") in the published literature. Variables such as formulation type, time of treatment, period after treatment during which milk production was recorded, outcome measure recorded and parity were associated with the trial outcome (but only accounted for small amounts of the unexplained variance between studies). Although guidelines for anthelmintic treatment in adult dairy cows could not be stated from the present meta-analysis, an important variation in treatment response was observed—suggesting that if a reliable diagnostic test for gastrointestinal parasitism in adult cows became available, a beneficial treatment effect could be expected in herds classified as having parasite problems.

## References

Agneessens, J., Claerebout, E., Dorny, P., Borgsteede, F.H., Vercruysse, J., 2000. Nematode parasitism in adult dairy cows in Belgium. Vet. Parasitol. 90, 83–92.

Alvarez, E., Greco, J.A., Alberdi, J.G., Romano, A., 1977. Anthelmintic treatment of cattle by the 'spot' method, with levamisole. Gaceta Veterinaria 39, 18–22.

Barger, I.A., 1979. Milk production of grazing dairy cattle after a single anthelmintic treatment. Aust. Vet. J. 55, 68–70.

Barger, I.A., Lisle, K.A., 1982. Milk production of grazing dairy cows given monthly anthelmintic treatment. Aust. Vet. J. 58, 245–248.

Beatty, J.F., Arnold, B.L., Custer, E.W., McGee, W.H., Daniels, J.W., 1975. Effect of a coumaphos anthelmintic on production and quality. J. Dairy Sci. 58, 144.

Begg, C.B., Mazumdar, M., 1994. Operating characteristics of a rank correlation test for publication bias. Biometrics 50, 1088–1101.

Bell, R.R., 1980. Effect of thiabendazole treatment on dairy cows in Texas. In: Proceedings of the 25th Annual Meeting of the American Association of Veterinary Parasitology, Washington, USA, p. 28.

Bhongade, H.G., Sarode, D.B., Rode, A.M., Sapre, V.A., 1993. Effect of anthelmintic therapy on haematobiochemical profiles of dairy cows. Indian J. Vet. Med. 13, 75–76.

Biondani, C.A., Steffan, P., 1988. Efecto de los parasitos gastrointestinales sobre la produccion lactea en rodeos lecheros. Vet. Argentina 42, 116–127.

Bisset, S.A., Marshall, E.D., Morrison, L., 1987. Economics of a dry-cow anthelmintic drenching programme for dairy cows in New Zealand. Part 1. Overall response in 47 herds. Vet. Parasitol. 26, 107–118.

Bliss, D.H., Jones, R.M., Conder, D.R., 1982. Epidemiology and control of gastrointestinal parasitism in lactating, grazing adult dairy cows using a morantel sustained release bolus. Vet. Rec. 110, 141–144.

Bliss, D.H., Todd, A.C., 1973. Milk production by Wisconsin dairy cattle after deworming with BAYMIX. Vet. Med. Small Anim. Clin. 68, 1034–1038.

Bliss, D.H., Todd, A.C., 1974. Milk production by Wisconsin dairy cattle after deworming with thiabendazole. Vet. Med. Small Anim. Clin. 69, 638–640.

Bliss, D.H., Todd, A.C., 1976. Milk production by Vermont dairy cattle after deworming. Vet. Med. Small Anim. Clin. 71, 1251–1254.

Block, E., Gadbois, P., 1986. Efficacy of morantel tartrate on milk production of dairy cows: a field study. J. Dairy Sci. 69, 1135–1140.

Block, E., McDonald, W.A., Jackson, B.A., 1987. Efficacy of Levamisol on milk production of dairy cows: a field study. J. Dairy Sci. 70, 1080–1085.

Borgsteede, F.H., Tibben, J., Cornelissen, J.B., Agneessens, J., Gaasenbeek, C.P., 2000. Nematode parasites of adult dairy cattle in the Netherlands. Vet. Parasitol. 89, 287–296.

Brown, M.A., Maniscalco, V.J., 1974. Effects on milk production and internal parasites of dairy cattle from a ration supplemented with a parasiticide. The Southwestern Veterinarian Winter, pp. 51–53.

Carrier, J., DesCoteaux, L., Smith, R.A., 1999. Effect of an eprinomectin treatment at fall housing of milk production of dairy cows in Quebec. In: Proceedings of the 32nd Annual Conference American Association of Bovine Practitioners, Nashville, TN, USA, September 23–26, 1999, pp. 234–235.

Corba, J., Reis, T., Gruebler, R., 1980. Effect of dehelmintization in dairy cattle with subclinical helminthoses on milk production. Helminthologia 17, 219–224.

Deeks, J.J., Altman, D.G., Bradbrun, M.J., 2001. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Systematic Reviews in Health Care: Meta-analysis in Context. BMJ Books, London, pp. 285–312.

De Rond, J.C., de Jong, R., Boon, J.H., Brouwer, B., 1990. Influence of gastro-intestinal nematodes on the productivity of dairy cattle in the wet highlands of Sri Lanka. Trop. Anim. Health Prod. 22, 135–143.

DesCoteaux, L., Doucet, M., Caldwell, V., 2001. Evaluation of the impact of parasite control with the IVOMEC(R) SR Bolus given at breeding age on first lactation yield in Holstein heifers. Vet. Parasitol. 98, 309–314.

Duval, S., Tweedie, R., 2000. A nonparametric "Trim and Fill" method of accounting for publication bias in meta-analysis. J. Am. Stat. Assoc. 95, 89–98.

Eddi, C., Muniz, R.A., Caracostantogolo, J., Errecalde, J.O., Rew, R.S., Michener, S.L., McKenzie, M.E., 1997. Comparative persistent efficacy of doramectin, ivermectin and fenbendazole against natural nematode infections in cattle. Vet. Parasitol. 72, 33–41.

Egger, M., Davey Smith, G., 2001. Principles of and procedures for systematic reviews. In: BMJ Books (Ed.), Systematic Reviews in Health Care: Meta-analysis in Context, London, pp. 23–43.

Egger, M., Smith, G.D., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. Brit. Med. J. 315, 629–634.

Eysker, M., 1997. Some aspects of inhibited development of trichostrongylids in ruminants. Vet. Parasitol. 72, 265–272.

Eysker, M., Eilers, C., 1995. Persistence of the effect of a moxidectin pour-on against naturally acquired cattle nematodes. Vet. Rec. 137, 457–460.

Eysker, M., Ploeger, H.W., 2000. Value of present diagnostic methods for gastrointestinal nematode infections in ruminants. Parasitology 120 (Suppl.), S109–S119.

Fetrow, J., Johnstone, C., Bartholomew, R., 1985. Production responses of lactating dairy cows and heifers given thiabendazole at parturition. Am. J. Vet. Res. 46, 48–52.

Fisher, L.J., 1980. The economic response of lactating cows to treatment for parasites. Can. J. Anim. Sci. 60, 1063–1064.

Fisher, L.J., MacNeill, A.C., 1982. The response of lactating cows and growing heifers to treatment for parasites. Can. J. Anim. Sci. 62, 481–486.

Fox, M.T., 1979. Deworming of cows—What are the benefits? Vet. Rec. 105, 315–316.

Fox, M.T., Jacobs, D.E., 1984. Observations on the effect of levamisole treatment on the production of dairy cows in England. Anim. Prod. 38, 15–22.

Frechette, J.L., Lamothe, P., 1981. Milk production effect of a morantel tartrate treatment at calving in dairy cows with subclinical parasitism. Can. Vet. J. 22, 252–254.

Froyd, G., 1973. Strategic treatment against subclinical parasitism. Helminthologia 14, 377–384.

Gasbarre, L.C., Stout, W.L., 1998. An ounce of prevention equals pounds of milk. Agric. Res. Washington 46, 10–11.

Gibbs, H.C., 1980. Effect of thiabendazole treatment of lactating dairy cows in Maine. In: Proceedings of the 25th Annual Meeting of the American Association of Veterinary Parasitology, Washington, USA, p. 27.

Glenn, J.S., Baker, N.F., Franti, C.E., Ver Steeg, J.D., 1982. Anthelmintic treatment of nonpastured dairy cows in California. J. Dairy Sci. 65, 2006–2010.

Gouffe, D., Raoult, J., Vallet, A., 1984. Strongyloses gastro-intestinales et production laitiere. Revue Med. Vet. 135, 779–782.

Gremillet, J.P., 1981. The use of thiabendazole to augment milk production. Bulletin Mensuel De La Societe Veterinaire Pratique De France 65, 603–610.

Gross, S.J., Ryan, W.G., Ploeger, H.W., 1999. Anthelmintic treatment of dairy cows and its effect on milk production. Vet. Rec. 144, 581–587.

Harris, B., Wilcox, C.J., 1976. Effect of anthelmintics on milk production. J. Dairy Sci. 59, 20–21.

Heider, L.E., Courtney, C.H., Herd, R. 1980. The effect of thiabendazole treatment on dairy cows in Ohio. In: Proceedings of the 25th Annual Meeting of the American Association of Veterinary Parasitology, Washington, USA, p. 28.

Hoste, H., Le Frileux, Y., Pommaret, A., 2002. Comparison of selective and systematic treatments to control nematode infection of the digestive tract in dairy goats. Vet. Parasitol. 106, 345–355.

Kloosterman, A., Albers, G.A.A., 1982. The effect of anthelmintic treatment or artificial trichostrongylid infection on milk production of cows. Parasitology 84, xxxiii–xxxxiv.

Kloosterman, A., Ploeger, H.W., Pieke, E.J., Lam, T.J.G.M., Verhoeff, J., 1996. The value of bulk milk ELISA Ostertagia antibody titres as indicators of milk production response to anthelmintic treatment in the dry period. Vet. Parasitol. 64, 197–205.

Mathews, G.L., Gray, R.M., McGowan, A.A., 1983. Effect of anthelmintic treatment immediately after calving on milk production. Aust. Vet. J. 60, 116–119.

McBeath, D.G., Dean, S.P., Preston, N.K., 1979. The effect of a preparturient febendazole treatment on lactation yield in dairy cows. Vet. Rec. 105, 507–509.

McPherson, W.B., Gogolewski, R.P., Slacek, B., Familton, A.S., Gross, S.J., Maciel, A.E., Ryan, W.G., 2001. Effect of a peri-parturient eprinomectin treatment of dairy cows on milk production. New Zeal. Vet. J. 49, 106–110.

McPherson, W.B., Slacek, B., Familton, A., Gogolewski, R.P., Cramer, R.P., Gross, S.J., 1999. The benefit of topical eprinomectin on milk production in dairy cattle. In: Proceedings of the 17th International Conference of the World Association for the Advancement of Veterinary Parasitologists, Copehagen, Denmark.

McQueen, I.P.M., Cottier, K., Hewitt, S.R., Wright, D.F., 1977. Effects of anthelmintics on dairy cow yields. New Zeal. J. Exp. Agric. 5, 115–119.

Michel, J.F., Richards, M., Altman, J.F.B., Mulholland, J.R., Gould, C.M., Armour, J., 1982. Effect of anthelmintic treatment on the milk yield of dairy cows in England, Scotland and Wales. Vet. Rec. 111, 546–550.

Miller, J.E., Baker, N.F., Farver, T.B., 1986. Anthelmintic treatment of pastured dairy cattle in California. Am. J. Vet. Res. 47, 2036–2040.

Moher, D., Pham, B., Jones, A., Cook, D.J., Jadad, A.R., Moher, M., Tugwell, P., Klassen, T.P., 1998. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 352, 609–613.

Moore, E.D., Owen, J.R., Dowlen, H.H., Haws, L.D., Richardson, D.O., Smith, J.W., Bennett, S.E., 1974. Comparison of anthelmintic treatments for replacement dairy heifers and dairy cows. Southern Div Memphis, Tennessee, 4–7 February, 1974. J. Dairy Sci. 57, 145.

Morhain, A., Legrand, J., 1981. Field tests with thiabendazole as a galactogen. Bulletin Mensuel De La Societe Veterinaire Pratique De France 65, 615–620.

Murphy, A., 1998. The effect of treatment with moxidectin, a long-acting endectocide, on milk production in lactating dairy cows. In: Proceedings of the XXth World Association for Buiattrics Congress, pp. 35–45.

Nødtvedt, A., Dohoo, I., Sanchez, J., Conboy, G., DesCoteaux, L., Keefe, G.P., Leslie, K., Campbell, J., 2002a. The use of negative binomial modelling in a longitudinal study of gastrointestinal parasite burdens in Canadian dairy cows. Can. J. Vet. Res. 66, 249–257.

Nødtvedt, A., Dohoo, I., Sanchez, J., Conboy, G., DesCoteaux, L., Keefe, G.P., 2002b. Increase in milk yield following eprinomectin treatment at calving in pastured dairy cattle. Vet. Parasitol. 105, 191–206.

O'Farrell, K.J., Downey, N.E., Sherington, J., 1986. The effect of anthelmintic treatment at calving on the subsequent milk production characteristics of dairy cows. Irish Vet. J. 40, 116–123.

Pfister, K., Reist, M., Meditna, D., 2001. The effect of eprinomectin or trichlorfon on milk yield of dairy cattle. In: Proceedings of the 18th International Conference of the World Association for the Advancement of Veterinary Parasitologists, Stresa, Italy.

Ploeger, H.W., Kloosterman, A., Bargeman, G., Wuijckhuise, L.V., Brink, R.R., Van den, B.R., 1990a. Milk yield increase after anthelmintic treatment of dairy cattle related to some parameters estimating helminth infection. Vet. Parasitol. 35, 103–116.

Ploeger, H.W., Kloosterman, A., Borgsteede, F.H.M., 1990b. Effect of anthelmintic treatment of second-year cattle on growth performance during winter housing and first lactation yield. Vet. Parasitol. 36, 311–323.

Ploeger, H.W., Schoenmaker, G.J.W., Kloosterman, A., Borgsteede, F.H.M., 1989. Effect of anthelmintic treatment of dairy cattle on milk production related to some parameters estimating nematode infection. Vet. Parasitol. 34, 239–253.

Pluimers, E.J., 1979. Milk production increase following treatment of Dutch dairy cattle with thiabendazole. Vet. Quart. 1, 82–89.

Pouplard, L., 1978. Anthelmintic treatment of dairy cows. Vet. Rec. 103, 434.

Prosl, H., Supperer, R., Jones, R.M., Lockwood, P.W., Bliss, D.H., 1983. Morantel sustained release bolus: a new approach for the control of trichostrongylosis in Austrian cattle. Vet. Parasitol. 12, 239–250.

Rosenthal, R., DiMatteo, M.R., 2001. Meta-analysis: recent developments in quantitative methods for literature reviews. Annu. Rev. Psychol. 52, 59–82.

Sanchez, J., Dohoo, I., Nødtvedt, A., Markham, F., Leslie, K., DesCoteaux, L., Campbell, J., Keefe, G.P., 2002. A longitudinal study of gastrointestinal parasites in Canadian dairy farms. The value of an indirect *Ostertagia ostertagi* ELISA as monitoring tool. Vet. Parasitol. 107, 209–226.

Sanyal, P.K., Singh, D.K., Knox, M.R., 1992. The effect of peri-parturient anthelmintic treatment on the productivity of dairy cattle in subtropical western India. Vet. Res. Commun. 16, 445–451.

Sanyal, P.K., Srivastava, S.M., Panchal, A.G., Singh, D.K., 1995. Effect of feeding fenbendazole incorporated urea molasses block on nematode infection and milk yield of dairy cattle. J. Vet. Parasitol. 9, 11–16.

Spence, S.A., Fraser, G.C., Chang, S., 1996. Responses in milk production to control of gastrointestinal nematode and paramphistome parasites in dairy cattle. Aust. Vet. J. 74, 456–459.

Sommefeldt, J.L., Clark, A.K., Hugghins, E.J., Shultz, J.B., Illg, D.J., 1986. Responses to controlling gastrointestinal parasitism in dairy cattle 69, 2723–2727.

Spence, S.A., Fraser, G.C., Dettmann, E.B., Battese, D.F., 1992. Production responses to internal parasite control in dairy cattle. Aust. Vet. J. 69, 217–220.

Stata Corporation, 2001. Stata Statistical Software, College Station, TX.

Sterne, J.A., Egger, M., Davey Smith, G., 2001. Investigating and dealing with publication and other biases. In: Systematic Reviews in Health Care: Meta-analysis in Context. BMJ Books, London, pp. 189–208.

Takagi, H., Block, E., 1986. Effects of feeding coumaphos to dairy cows at various stages of lactation on subclinical parasite infection and milk production. Can. J. Anim. Sci. 66, 141–150.

Tharaldsen, J., Helle, O., 1989. The effect of periparturient treatment with fenbendazole on the milk production of cows. Acta Vet. Scand. 30, 247–252.

Thomas, G.W., Barton, N.J., McGowan, A.A., Mickan, F.J., Miller, G., James, R.E., 1984. Effect of whole herd anthelmintic treatment on milk production of dairy cows. Res. Vet. Sci. 36, 266–269.

Thomas, R.J., Rowlinson, P., Nansen, P., Jorgensen, R.J., Soulsby, E.J.L., 1981. An evaluation of the anthelmintic treatment in a dairy herd. In: Nansen, P., Jorgensen, R.J., Soulsby, E.J.L. (Eds.), In epidemiology and control of nematodiasis in cattle, EEC, Brussels ECSC, pp. 101–115.

Thompson, S.G., Higgins, J.P., 2002. How should meta-regression analyses be undertaken and interpreted? Stat. Med. 21, 1559–1573.

Thompson, S.G., Sharp, S.J., 1999. Explaining heterogeneity in meta-analysis: a comparison of methods. Stat. Med. 18, 2693–2708.

Todd, A.C., Bliss, D., Grisi, L., Crowley, J.W., 1978. Milk production by dairy cattle in Pennsylvania and North Carolina after deworiming (treatment at freshening and systematically over the first three months of lactation). Vet. Med. Small Anim. Clin. 73, 614–619.

Todd, A.C., Bliss, D.H., Meyers, G.H., 1975. Milk production increases following treatment of subclinical parasitisms in Wisconsin dairy cattle. New Zeal. Vet. J. 23, 59–62.

Todd, A.C., Myers, G.H., Bliss, D., Cox, D.D., 1972. Milk production in Wisconsin dairy cattle after anthelmintic treatment. Vet. Med. Small Anim. Clin. 67, 1233–1236.

van Adrichem, P.W.M., Shaw, J.C., 1977. Effects of gastrointestinal nematodiasis on the productivity of monozygous twin cattle. 2. Growth performance and milk production. J. Anim. Sci. 46, 423–429.

Vercruysse, J., Claerebout, E., 2001. Treatment vs. non-treatment of helminth infections in cattle: defining the threshold. Vet. Parasitol. 98, 195–214.

Walsh, A., Younis, P.J., Morton, J.M., 1995. The effect of ivermectin treatment of late pregnant dairy cows in south-west Victoria on subsequent milk production and reproductive performance. Aust. Vet. J. 72, 201–207.

Wilk, J.C., Porterfield, I.D., McDaniel, B.T., 1980. Effects of the use of thiabendazole at calving in Holsteins and Jerseys. J. Dairy Sci. 63.

Wilkinson, A.C.R., 1992. Husk in heifers. Vet. Rec. 131, 567–568.

Yazwinski, T.A., Tucker, C., Copeland, S., Yazwinski, T., Guerino, F., 1999. Dose confirmation of moxidectin pour-on against natural nematode infections in lactating dairy cows. Vet. Parasitol. 86, 223–228.