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ORIGINAL PAPER

Veterinary homeopathy: meta-analysis of randomised placebo-controlled trials

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Background: **Meta-analysis of randomised controlled trials (RCTs) of veterinary homeopathy has not previously been undertaken. For all medical conditions and species collectively, we tested the hypothesis that the outcome of homeopathic intervention (treatment and/or prophylaxis, individualised and/or non-individualised) is distinguishable from corresponding intervention using placebos.**
Methods: **All facets of the review, including literature search strategy, study eligibility, data extraction and assessment of risk of bias, were described in an earlier paper. A trial was judged to comprise reliable evidence if its risk of bias was low or was unclear in specific domains of assessment. Effect size was reported as odds ratio (OR). A trial was judged free of vested interest if it was not funded by a homeopathic pharmacy. Meta-analysis was conducted using the random-effects model, with hypothesis-driven sensitivity analysis based on risk of bias.**
Results: **Nine of 15 trials with extractable data displayed high risk of bias; low or unclear risk of bias was attributed to each of the remaining six trials, only two of which comprised reliable evidence without overt vested interest. For all *N* = 15 trials, pooled OR = 1.69 [95% confidence interval (CI), 1.12 to 2.56]; *P* = 0.01. For the *N* = 2 trials with suitably reliable evidence, pooled OR = 2.62 [95% CI, 1.13 to 6.05]; *P* = 0.02).**
Conclusions: **Meta-analysis provides some very limited evidence that clinical intervention in animals using homeopathic medicines is distinguishable from corresponding intervention using placebos. The low number and quality of the trials hinders a more decisive conclusion.** *Homeopathy* (2015) **104**, 3–8.

Keywords: Veterinary homeopathy; Randomised controlled trials; Placebo control; Systematic review; Meta-analysis

Introduction

Our group has previously identified 18 randomised placebo-controlled trials of veterinary homeopathy, published in the peer-reviewed literature and eligible for systematic review.[1,2] Risk-of-bias assessment of those trials highlighted their poor quality overall, and noted only two trials with reliable evidence and without obvious vested interest.[2] Our condition-specific analysis concluded on the findings of each of those two trials: individualised homeopathic treatment did not have a beneficial effect on bovine mastitis[3]; homeopathic *Coli* had a prophylactic effect on porcine diarrhoea.[4] Because of these mixed results from so few suitable trials, we were unable to reach generalisable conclusions about the impact of any particular homeopathic intervention in any given medical condition in animals.

The present paper therefore focuses on broader questions about the clinical impact of veterinary homeopathy. We have examined the same 18 trials,[2] across all medical conditions and species and, importantly, by style of homeopathic intervention. Accepting, *a priori*, that the material would comprise both clinical and statistical heterogeneity,[5] we have tested each of the following hypotheses:

1. **Homeopathic treatment or prophylaxis overall (all 18 trials)**: Clinical intervention in animals using homeopathic medicines is distinguishable from corresponding intervention using placebos.

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2. **Homeopathic treatment overall**: Homeopathic treatment in animals is distinguishable from the same approach using placebos.
   a. **Individualised homeopathic treatment**: Homeopathic treatment is distinguishable from the same individualised approach using placebos.
   b. **Non-individualised homeopathic treatment**: Treatment using a particular homeopathic medicine is distinguishable from the same approach using a placebo.
3. **Homeopathic prophylaxis overall**: Homeopathic prophylaxis in animals is distinguishable from the same approach using placebos.
   a. **Individualised homeopathic prophylaxis**: Homeopathic prophylaxis is distinguishable from the same individualised approach using placebos.
   b. **Non-individualised homeopathic prophylaxis**: Prophylaxis using a particular homeopathic medicine is distinguishable from the same approach using a placebo.

Methods

Matters connected with study eligibility, research design categories and the literature search strategy were described in detail in our recent papers.[1,2] Only brief descriptions are therefore given here, with additional information that is specific to the methods used for the present paper.

Identifying papers for full data extraction

Eighteen records were previously identified as satisfying the key acceptance criteria for the present study: substantive report of clinical treatment or prophylaxis trial in veterinary homeopathic medicine, randomised, controlled by placebo, and published in a peer-reviewed journal.[1] The 18 studies comprise 12 treatment trials and six prophylaxis trials.

Data extraction and management

The authors of eligible randomised controlled trial (RCT) papers were not approached for clarification on unclear or missing facets of any of their methods or results; however, original authors' cross-reference to their previously published study methods were eligible for follow-up and taken into account as appropriate. For each of two assessors (RTM and JC) working independently, relevant data were extracted and then recorded using a standardised data collection format (Microsoft *Excel*).

None of the 18 papers reported more than one trial. For a paper reporting an RCT that involved >2 groups of subjects, we focused data extraction on *only one pair of groups* as follows: treatment in preference to prophylaxis; placebo control in preference to other-than-placebo control. For studies that comprised more than one homeopathy group, the total sample size that we cite reflects the total numbers of subjects in the relevant homeopathy groups *combined*.[6]

Study appraisal

Risk of bias per trial: Each trial was assessed against seven pre-defined judgmental criteria[2]: *domain I*, the method used to generate the random sequence; *domain II*, the method of allocation concealment used to implement the random sequence; *domain IIIA*, the blinding of trial personnel, including animal owner as appropriate; *domain IIIB*, the blinding of outcome assessors; *domain IV*, whether all the randomised patients are accounted for in the analysis; *domain V*, whether there is evidence of selective outcome reporting[a]; *domain VI*, whether there is evidence of other bias, such as extreme data imbalance at baseline.[7]

An overall classification of 'low risk of bias', 'uncertain risk of bias' or 'high risk of bias' was then applied to each trial. A trial with overall low risk of bias comprised 'reliable evidence'. For a trial that did not display high risk of bias, we regarded its evidence as *reliable* if the study was assessed as free of bias for each of domains I, IIIA, IIIB and IV. Finally, importance was placed on trials with reliable evidence and were not explicitly funded, directly or indirectly, by a homeopathic pharmacy (there was no overt vested interest in the trial's findings).[2]

Outcome assessment and reporting

As previously described,[2] for each trial we identified the 'main outcome measure' using a refinement of approaches adopted by others.[8,9]

Meta-analysis

Summary measures for 'main outcome': For each eligible trial, the 'effect size' was taken as the difference between the homeopathy and the placebo groups at our pre-determined end-point of the trial, as follows[10]:

- For **dichotomous measures**: odds ratio (OR), with 95% confidence interval (CI);
- For **continuous measures**: standardised mean difference (SMD), with 95% CI.

If the original paper did not provide adequate information on our designated main outcome measure to enable data extraction for meta-analysis, we described that trial's outcome as 'not estimable': a further, estimable, outcome was not sought.

All calculations and analyses were performed using Review Manager 5.2 (Cochrane Collaboration). Given our anticipation of heterogeneous data for intervention effects, the random-effects (rather than fixed-effects) model was used for all meta-analyses.[5] For meta-analyses requiring the merging of dichotomous and continuous data, we re-expressed SMD of relevant RCT data as OR.[5,11]

Hypothesis-driven analysis: For all species per category we aimed to determine summary statistics for:

[a] No study protocol existed for any of the studies: domain V was assessed as described in Reference 2. For the purposes of the current paper, we would have been entitled to reassess a trial as high risk of bias in domain V if the main outcome data were not extractable for meta-analysis; however, to ensure a unified approach with that of Reference 2, we opted not to carry out such reassessment.

1) : Effect of homeopathic treatment or prophylaxis overall: ***N* = 18**.
2) : Effect of homeopathic treatment: ***N* = 12**.
   2a) : Effect of individualised homeopathic treatment: ***N* = 2**.
   2b) : Effect of non-individualised homeopathic treatment: ***N* = 10**.
3) : Effect of (non-individualised) homeopathic prophylaxis: ***N* = 6**.
   (No trials of individualized homeopathic prophylaxis were available)

Heterogeneity and reporting biases: The degree of heterogeneity in the meta-analysis data (all eligible trials) was judged from the asymmetry coefficient, I^2, from Chi-square test with its associated *P* value, and from visual interpretation of the funnel plot. The latter was also used to infer the presence or absence of reporting biases.[12]

Sensitivity analysis: Primary analyses were carried out using the data extracted from trials with reliable evidence and with no overt vested interest (see above).

Results

Demographic details

Table 1 summarises key information, including the medical condition and species studied in each trial. Our associated paper provides more complete details.[2]

Risk of bias, reliable evidence and vested interest

Eleven of the 18 trials were each classified high risk of bias; the remaining seven trials were either low or uncertain risk of bias.[2] Three trials were designated reliable evidence: Hektoen et al. 2004[3]; Camerlink et al. 2010[4]; Cracknell & Mills 2008.[13] The first two of these three trials were designated reliable evidence with no overt vested interest (see Table 1).

Meta-analysis

Data were not extractable for meta-analysis from three trial reports: Andersson et al. 1997[14]; Holmes et al. 2005[15]; Danieli et al. 2009.[16] Data from 15 trials were therefore available for meta-analysis (Table 1): nine of these 15 trials displayed high risk of bias; unclear or low risk of bias was attributed to each of the remaining six trials, two of which were deemed reliable evidence and with no overt vested interest (Hektoen et al. 2004[3]; Camerlink et al. 2010[4]).

Webappendix 1 and Webappendix 2 give, respectively, the original forest plots of data from trials with dichotomous and with continuous outcome data.

Figure 1 shows the forest plot of all data (dichotomous plus continuous outcomes). The pooled OR was 1.69 [95% CI, 1.12 to 2.56]; $N = 15$; $P = 0.01$, a significant difference in favour of homeopathy.

Heterogeneity and reporting biases:

- Asymmetry coefficient, $I^2 = 67\%$; Chi-square (14 degrees of freedom) = 43.07 ($P < 0.001$) — see also Figure 1.
  - The variability in the estimated pooled OR is therefore relatively high, and so our use of the random-effects model was confirmed as appropriate.
- The funnel plot is shown in Figure 2. One extreme outlier was evident: an exploratory sensitivity analysis (removal of the relevant trial, A11 Wolter) was therefore carried out:

Table 1 Summary of demographic data for 18 randomised controlled trials of veterinary homeopathy

No.	*First author [ref]*	*Year*	*Condition*	*Species*	*Risk of bias*	*Reliable evidence*	*Free of vested interest*	*Extractable data for analysis*
Individualised homeopathy/Treatment								
A01	Hektoen [3]	2004	Mastitis	Bovine	Low	Yes	Unclear	Yes
A02	Werner [22]	2010	Mastitis	Bovine	High	No	Unclear	Yes
Non-individualised homeopathy/Treatment								
A03	Andersson [14]	1997	Mastitis	Bovine	High	No	No	No
A04	Cracknell [13]	2008	Fear of firework noises	Canine	Unclear	Yes	No	Yes
A05	de Verdier [23]	2003	Diarrhoea	Bovine	High	No	No	Yes
A06	Fidelak [24]	2007	Infertility	Bovine	High	No	Unclear	Yes
A07	Hielm-Björkman [25]	2009	Osteoarthritis	Canine	Unclear	No	No	Yes
A08	Holmes [15]	2005	Mastitis	Bovine	Unclear	No	Yes	No
A09	Kayne [26]	1994	Diarrhoea	Bovine	High	No	No	Yes
A10	Searcy [27]	1995	Mastitis	Bovine	High	No	Unclear	Yes
A11	Wolter [28]	1966	Induction of farrowing	Porcine	High	No	No	Yes
A28	Williamson [29]	1995	Infertility	Bovine	High	No	No	Yes
Non-individualised homeopathy/Prophylaxis								
A22	Albrecht [30]	1999	Infectious diseases (respiratory)	Porcine	High	No	No	Yes
A23	Arlt [31]	2009	Endometritis	Bovine	High	No	No	Yes
A24	Camerlink [4]	2010	Diarrhoea	Porcine	Unclear	Yes	Unclear	Yes
A25	Danieli [16]	2009	Metabolic disturbance postpartum	Caprine	High	No	Unclear	No
A26	Guajardo-Bernal [32]	1996	Growth rate	Porcine	Unclear	No	Unclear	Yes
A27	Soto [33]	2010	Reproductive performance	Porcine	Unclear	No	Unclear	Yes

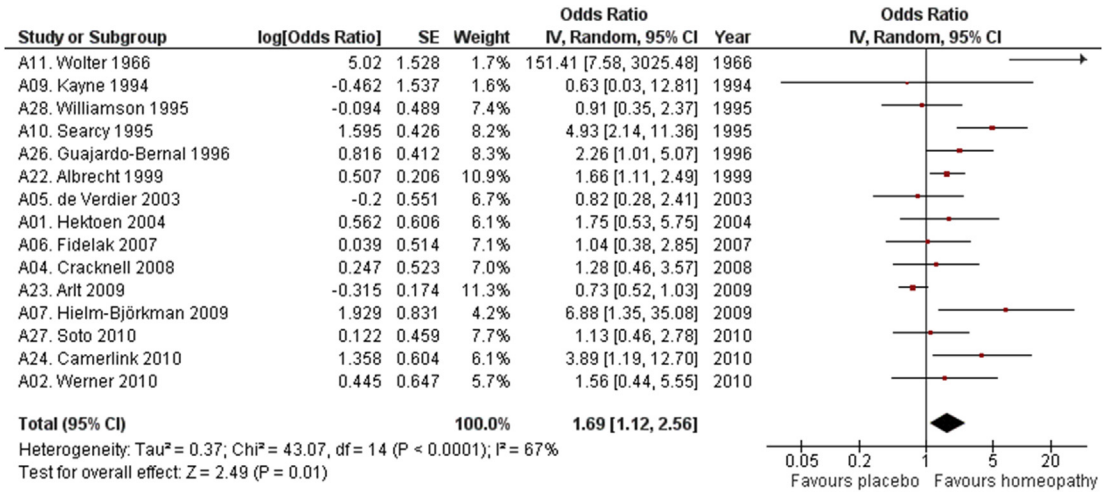

Figure 1 Forest plot of $N = 15$ trials, presented in chronological order of publication. Descriptive numbers (A01, A02, etc.) correspond with numbered references in the connected literature review paper.[1] SE: standard error of log[odds ratio]. IV: inverse variance. Random: random-effects model. 95% CI: 95% confidence interval. df: degrees of freedom. I^2: heterogeneity statistic].

- OR = 1.55 [95% CI, 1.07 to 2.26]; $N = 14$; $P = 0.02$;
- Asymmetry coefficient, $I^2 = 61\%$; Chi-square (13 degrees of freedom) = 33.38 ($P = 0.001$).
- Since no marked differences were observed in comparison with data for $N = 15$, the outlier was not removed from any of our analyses.
- Other reporting biases were not evident.

Sensitivity analysis: Sensitivity analysis, based on trials' risk of bias, is shown in Table 2. With our primary conclusions based on reliable evidence and no overt vested interest, there was evidence in favour of *Hypothesis 1* (treatment or prophylaxis: OR = 2.62 [95% CI, 1.13 to 6.05]; $N = 2$; $P = 0.02$) and for *Hypothesis 3* (non-individualised prophylaxis: OR = 3.89 [95% CI, 1.19 to 12.7]; $N = 1$; $P = 0.02$). The favourable evidence for both these hypotheses was retained when conclusions were based on trials at low/unclear risk of bias (Table 2).

Favourable evidence for *Hypothesis 1* was absent when analysis was limited to trials classified as high risk of bias ($N = 9$): OR = 1.50 [95% CI, 0.84 to 2.66]; $P = 0.17$ (data not tabulated).

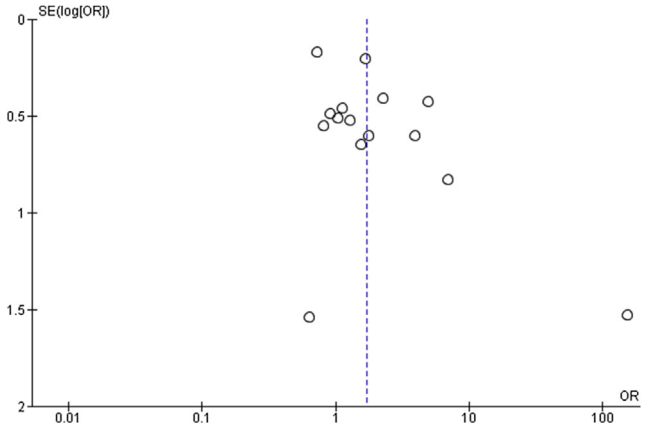

Figure 2 Funnel plot of $N = 15$ trials.

No reliable evidence was found with regard to *Hypotheses 2*, *2a* or *2b* (treatment).

Discussion

The caveats associated with 'global' meta-analysis of highly heterogeneous data have been emphasised by our group.[17] Although it was accepted, *a priori*, that only limited interpretation of heterogeneous veterinary RCT data would be feasible, there is precedent for this style of approach from comprehensive meta-analysis of homeopathy RCTs in human subjects.[8,9,17] It was also important to examine whether, generically, a given style or styles of homeopathic intervention might reveal a significant pooled effect size that was not primarily dependent on medical condition.

The results of our analysis that yielded a statistically significant effect of homeopathy (OR = 1.69 [95% CI, 1.12 to 2.56]; $N = 15$; $P = 0.01$) must be interpreted with extreme caution. Our sensitivity analysis, which retained only the RCTs with low/unclear risk of bias, or only those with reliable evidence and no overt vested interest, contains too few and dissimilar trials to permit robust positive conclusions. Moreover, an OR less than approximately 2 may be regarded as a small clinical effect size.[2] The nature of our positive data therefore prevents us from confidently accepting *Hypothesis 1* (two RCTs re homeopathic intervention overall) or *Hypothesis 3* (1 RCT re non-individualised prophylaxis). These important caveats about number and study quality mirror our concerns about the same trials analysed individually.[2] Indeed, other attributes of the studies are also problematic including, under *Hypothesis 3*, that the single trial with reliable evidence was burdened with a large CI and an indirect homeopathic approach *via* the sows.[4]

No significant effect was noted for *individualised treatment*, for *non-individualised treatment*, or for *treatment overall* (*Hypotheses 2*, *2a* and *2b*), indicating that the tentative finding for *Hypothesis 1* above was due importantly to

Table 2 Pooled odds ratio and 95% confidence interval for hypothesis-based groups of trials, with sensitivity analysis on risk of bias and reliable evidence

Hypothesis		*All relevant trials*	*Trials at low or uncertain risk of bias*	*Reliable evidence*	*Reliable evidence plus no overt vested interest*
1)	Treatment or prophylaxis	1.69 [1.12, 2.56]; *N* = 15; *P* = 0.01	1.99 [1.25, 3.18]; *N* = 6; *P* = 0.004	1.96 [1.03, 3.76]; *N* = 3; *P* = 0.04	2.62 [1.13, 6.05]; *N* = 2; *P* = 0.02
2)	Treatment	1.91 [1.02, 3.59]; *N* = 10; *P* = 0.04	2.09 [0.87, 5.02]; *N* = 3; *P* = 0.10	1.46 [0.67, 3.18]; *N* = 2; *P* = 0.34	1.75 [0.53, 5.75]; *N* = 1; *P* = 0.35
2a)	Individualised treatment	1.66 [0.70, 3.95]; *N* = 2; *P* = 0.25	1.75 [0.53, 5.75]; *N* = 1; *P* = 0.35	1.75 [0.53, 5.75]; *N* = 1; *P* = 0.35	1.75 [0.53, 5.75]; *N* = 1; *P* = 0.35
2b)	Non-individualised treatment	2.06 [0.92, 4.62]; *N* = 8; *P* = 0.08	2.62 [0.51, 13.4]; *N* = 2; *P* = 0.25	1.28 [0.46, 3.57]; *N* = 1; *P* = 0.64	–
3)	Non-individualised prophylaxis	1.48 [0.84, 2.59]; *N* = 5; *P* = 0.17	2.01 [1.05, 3.85]; *N* = 3; *P* = 0.04	3.89 [1.19, 12.7]; *N* = 1; *P* = 0.02	3.89 [1.19, 12.7]; *N* = 1; *P* = 0.02

the positive influence of trials of non-individualised homeopathic prophylaxis. Such influence, from the results of RCTs whose prescribing approach might be viewed as controversial by some homeopathic practitioners,[18] further undermines the legitimacy of positive conclusions under *Hypothesis 1*.

It is interesting to note the limited influence of study quality on our overall meta-analysis results, with pooled OR typically not increasing in magnitude when we included trials at high risk of bias. Indeed, the high-risk trials themselves did not show a statistically significant effect size in favour of homeopathy (OR = 1.50; *P* = 0.17). It is recognised that lower-quality RCTs tend to have *larger* effect sizes than RCTs of higher quality[19,20]; our atypical findings might be due to the small proportion of higher-quality trials in our sample, thus narrowing the total range of study quality that we identified. In turn, the small proportion of higher-quality trials might partly be consequent on our stringent judgmental approach to risk-of-bias assessment.[17]

Despite the small total number of trials – and one extreme outlier – our funnel plot suggests that reporting biases did not make an important contribution to the findings overall. Absence of overt publication bias in the peer-reviewed literature, on which we focused analysis, suggests that our exclusion of the remaining, non-peer-reviewed, literature has not skewed our data in any meaningful way.

Our use of a single outcome measure per trial harmonises with the approach adopted in the three homeopathy meta-analyses cited above,[8,9,17] and for quality assessment of RCTs in conventional medicine.[20] This approach, together with our consistent use of meta-analysis-derived data per RCT, has revealed six (33%) out of the 18 trials, regardless of quality, that statistically significantly favoured homeopathy; no trial significantly favoured placebo. This analysis-based percentage of trials with positive findings contrasts with the much higher proportion of positives (63%) based on the original authors' own conclusions from RCTs of veterinary homeopathy,[21] which suggests that positive outcomes have been over-emphasised in some of the original reporting.

Conclusion

From meta-analysis of RCTs of veterinary homeopathy, there is some very limited evidence – and mainly from prophylaxis trials – that clinical intervention in animals using homeopathic medicines is distinguishable from corresponding intervention using placebos. Reflecting the mixed findings from our associated systematic review that focused on medical conditions,[2] the low number and quality of the trials hinders any decisive conclusion from meta-analysis.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.homp.2014.11.001.

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