

ORIGINAL PAPER

Randomised controlled trials of veterinary homeopathy: Characterising the peer-reviewed research literature for systematic review

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Introduction: Systematic review of the research evidence in veterinary homeopathy has never previously been carried out. This paper presents the search methods, together with categorised lists of retrieved records, that enable us to identify the literature that is acceptable for future systematic review of randomised controlled trials (RCTs) in veterinary homeopathy.

Methods: All randomised and controlled trials of homeopathic intervention (prophylaxis and/or treatment of disease, in any species except man) were appraised according to pre-specified criteria. The following databases were systematically searched from their inception up to and including March 2011: AMED; Carstens-Stiftung Homeopathic Veterinary Clinical Research (HomVetCR) database; CINAHL; Cochrane Central Register of Controlled Trials; Embase; Hom-Inform; LILACS; PubMed; Science Citation Index; Scopus.

Results: One hundred and fifty records were retrieved; 38 satisfied the acceptance criteria (substantive report of a clinical treatment or prophylaxis trial in veterinary homeopathic medicine randomised and controlled and published in a peer-reviewed journal), and were thus eligible for future planned systematic review. Approximately half of the rejected records were theses. Seven species and 27 different species-specific medical conditions were represented in the 38 papers. Similar numbers of papers reported trials of treatment and prophylaxis ($n=21$ and $n=17$ respectively) and were controlled against placebo or other than placebo ($n=18$, $n=20$ respectively). Most research focused on non-individualised homeopathy ($n=35$ papers) compared with individualised homeopathy ($n=3$).

Conclusion: The results provide a complete and clarified view of the RCT literature in veterinary homeopathy. We will systematically review the 38 substantive peer-reviewed journal articles under the main headings: treatment trials; prophylaxis trials. *Homeopathy* (2012) 101, 196–203.

Keywords: Veterinary homeopathy; Literature search strategy; Randomised controlled trials; Systematic review

Introduction

In its application to veterinary medicine, homeopathy has been reported in the treatment of many medical conditions in livestock and in companion animals.^{1–6} A number of randomised controlled trials (RCTs) in veterinary homeopathy are widely known,^{7–11} but a systematic review of this research evidence has never been attempted. The lack of such review to date may be partly a consequence of the diffuse and somewhat inaccessible

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nature of some of the relevant research literature. The availability of a published review of this nature would be important not only for veterinary homeopathy in particular but for homeopathic medicine more generally: "Animal studies may...be more useful than human studies in determining whether homeopathic remedies have specific effects in comparison with a placebo".¹²

Our group has ready access to an established and up-to-date library of research papers and books in homeopathy,¹³ and we therefore have the optimum base from which to undertake a major programme of systematic reviews of the relevant literature. The comprehensive search of the literature that we report in the present paper has ensured complete coverage.

In this review programme, we distinguish four principal attributes of research design and publication in homeopathy: (a) treatment *versus* prophylaxis; (b) controlled by placebo *versus* other than placebo (OTP); (c) individualised *versus* non-individualised (standardised) homeopathy; (d) peer-reviewed *versus* non-peer-reviewed sources. Each of the accepted RCTs will ultimately be characterised by full data extraction, including assessment of internal validity (risk of bias) against robust criteria using Cochrane methods.¹⁴ Trials published outside the peer-reviewed journal literature will not contribute to this particular programme of reviews.

Here we present the search methods, together with clear categorisation of retrieved records, which has enabled us to identify the literature that is eligible as acceptable for systematic review of RCTs in veterinary homeopathy. Such record is defined as a substantive report of a clinical treatment or prevention trial in veterinary homeopathic medicine (i.e. excluding animal experimentation) that is randomised and controlled and is published in a peer-reviewed journal. As well as informing our own programme of systematic reviews, the findings reported here will provide a uniquely organised source of references to assist those who are engaged in research in veterinary homeopathy.

Methods: literature search and identification of studies

Criteria for study eligibility

All randomised and controlled trials of homeopathic intervention (treatment and/or prophylaxis of disease, in any species except man) were eligible for review according to the inclusion/exclusion criteria outlined below.

Search methods for the identification of RCTs published in journal articles

The search aimed to target the entire world literature of RCTs in homeopathy (including non-peer-reviewed articles); it was not limited by language of publication. Only the search in PubMed focused specifically on animal-based studies; for outputs from other databases, veterinary research was identified by inspection.

Electronic searches: The following databases were searched from their inception up to and including March

2011: AMED (records available from 1985); Carstens-Stiftung Homeopathic Veterinary Clinical Research (HomVetCR) database (from 1934); CINAHL (from 1981); Cochrane Central Register of Controlled Trials (CENTRAL; from 1908); Embase (from 1980); Hom-Infom^a (from 1836); LILACS; PubMed (from 1950); Science Citation Index (from 1900); Scopus (from 1823).

The search strategy per database was as follows:

AMED: "(homeopath* OR homoeopath*) AND (random* OR placebo* OR singl* blind* OR doubl* blind* OR clinical trial*).af".

Carstens-Stiftung HomVetCR: Design = "Clinical Trial" or "Randomized Clinical Trial".

CINAHL: "(homeopath* OR homoeopath*) AND random* AND trial*".

CENTRAL (Clinical Trials Register): "homeopathy (MeSH)".

Embase: "(homeopath\$ OR homoeopath\$)" together with the Scottish Intercollegiate Guidelines Network (SIGN) search strategy for Embase.¹⁵

LILACS: "(homeopath\$ AND random\$)".

Hom-Infom: "(homeopath* OR homoeopath*) AND random* AND Article Type = Controlled Clinical Trial".

PubMed: (Cochrane Highly Sensitive Search Strategy¹⁶; "((homeopath* OR homoeopath*) AND ((randomized controlled trial[pt] OR (controlled clinical trial[pt]) OR (randomized[tiab] OR (placebo[tiab]) OR (clinical trials as topic[mesh:noexp]) OR (randomly[tiab] OR (trial[ti]))) NOT (humans [mh] NOT animals [mh]))".

Science Citation Index: "Topic = (homeopath* randomized)", plus all other pairs of terms using the variant spellings homoeopath* and randomized.

Scopus: "(homeopath* OR homoeopath*) AND (random* OR placebo* OR singl* blind* OR doubl* blind* OR clinical trial*)".

Other literature sources: to the above findings were added references identified as a RCT of veterinary homeopathy in a hand-search of reference lists in bibliography sections of appropriate papers. Experts in the field were also contacted to identify any other potentially relevant papers.

Attributes of research design and publication

(a) Treatment versus prophylaxis:

Treatment: a trial in which the first homeopathic intervention takes place after the onset of active symptoms associated with disease. Studies on sub-clinical disease or the control of recurrent disease ('secondary prevention') are categorised 'treatment' trials.

Prophylaxis: a trial on healthy individuals in which the homeopathic intervention aims to prevent the occurrence of disease *de novo* (i.e. 'primary prevention'). Studies using

^aThe Hom-Infom database comprises records of articles published up to 2004 only.

a strategy of primary prevention, with subsequent treatment as necessary, are categorised 'treatment' trials.

(b) *Placebo controlled versus other-than-placebo (OTP) controlled:*

Placebo controlled: a trial that describes the control group as 'placebo', 'dummy', 'sham', 'inactive control' or similar.

OTP controlled: a trial whose control is an active or minimally active intervention (proven conventional and/or complementary, non-homeopathic, medicine) or is untreated.

(c) *Individualised versus non-individualised homeopathy:*

Individualised homeopathy: any description that refers clearly to an intervention that involves the individual prescription of homeopathic medication for each animal in the study (and whether or not a case-taking interview with the owner is described). The intervention may involve a change of prescriptions in response to changing individual symptoms. This category includes trials in which individualised prescribing is limited within a defined range of pre-selected homeopathic medicines.

Non-individualised homeopathy: the term includes all interventions that have involved the same, specified, homeopathic medication being allocated to each and every animal in the study (e.g. herd or flock). This category includes trials in which a single herd- or flock-specific homeopathic prescription is identified based on profiling the individual animals that comprise the herd or flock.

(d) *Peer-reviewed versus non-peer-reviewed:*

The following have been automatically defined as 'not peer-reviewed': books; book chapters; abstracts/conference proceedings; theses/dissertations; newsletters; letters; reports.

The peer-review status of each relevant journal was identified by inspection of that journal's published information (website and/or printed version): the statement 'peer-reviewed' (or equivalent phrase) enabled the journal to be so designated for our review. We did not require the explicit statement that the peer review was external to the editorial board of the journal concerned. In cases where relevant information about the journal was absent or equivocal, its historical peer-review status was identified from *The Serials Directory*,¹⁷ where its presence in the *Peer Reviewed Index* enabled its designation 'peer-reviewed'; otherwise the journal was designated 'not peer-reviewed'.^b

Data collection and categorisation of articles (PRISMA¹⁸)

Screening: characterising search records as potentially eligible for systematic review: At this stage, the full texts

of articles were not sought: assessment was based solely on information available from each paper's title and/or abstract and/or database descriptor. Articles not reporting primary research were disregarded (except for the purpose of identifying references cited therein). Homeopathic pathogenetic ('provings') trials were also disregarded.

Publications of primary research identified as non-peer-reviewed were then removed (though they were later consulted, and in full text as required, for the assessment of repeat publication – see below).

Non-rejection of a record at this stage was based on evidence (explicit or implicit) that randomisation was used to determine group allocation and that there were control animals.

Full text scrutiny: characterising peer-reviewed records as RCTs potentially acceptable for full data extraction: The full texts of all remaining (peer-reviewed) articles were obtained; translation into a language that was familiar to the authors was carried out as required.

A paper was rejected if it was obvious that a group randomisation procedure was not part of the study design; alternate allocation, for example, was regarded as a non-randomised procedure.¹⁴ (Assessment of the precise nature and quality of group allocation [and other attributes of internal validity] is a facet of the subsequent review process and will be described in detail in the associated systematic review papers.) A paper was also rejected if it did not include a (non-homeopathy) control group of animals in the study design.

The following categories of article were also removed as non-eligible:

- Those reporting the same research as an earlier and/or less definitive publication.
- Research comprising healthy animals subjected experimentally to an illness (as opposed to being patients for veterinary homeopathic intervention).
- Non-substantive papers (1 page; 2 pages but with <500 words).

Finally, a paper was deemed non-eligible if the research used formulation(s) not described by the authors as 'homeopathic' and/or used a homeopathic dilution (including each component of complex formulations) of less than '1X' (or equivalent: e.g. 'D1' in continental Europe). Studies whose intervention combined homeopathy with another therapy were not excluded at this stage. Studies of anthroposophic or homotoxicological medicine fell within the inclusion criteria if the authors used the term 'homeopathic' in their description of the medicine(s) used. Likewise, studies that used 'homeopathic' medicines in the context of research in anthroposophic medicine or homotoxicology were not rejected.

Each record that remained complied with our eligibility criteria as acceptable for systematic review (see definition in Introduction). Each such article was characterised as follows:

- Species of animal;
- Medical condition investigated;

^b The category 'not peer-reviewed' includes any paper published in *The British Homoeopathic Journal* up to and including 1986, after which date the journal became peer-reviewed – Fisher P. A new editor. *Br J Hom* 1986; **75**: 123.

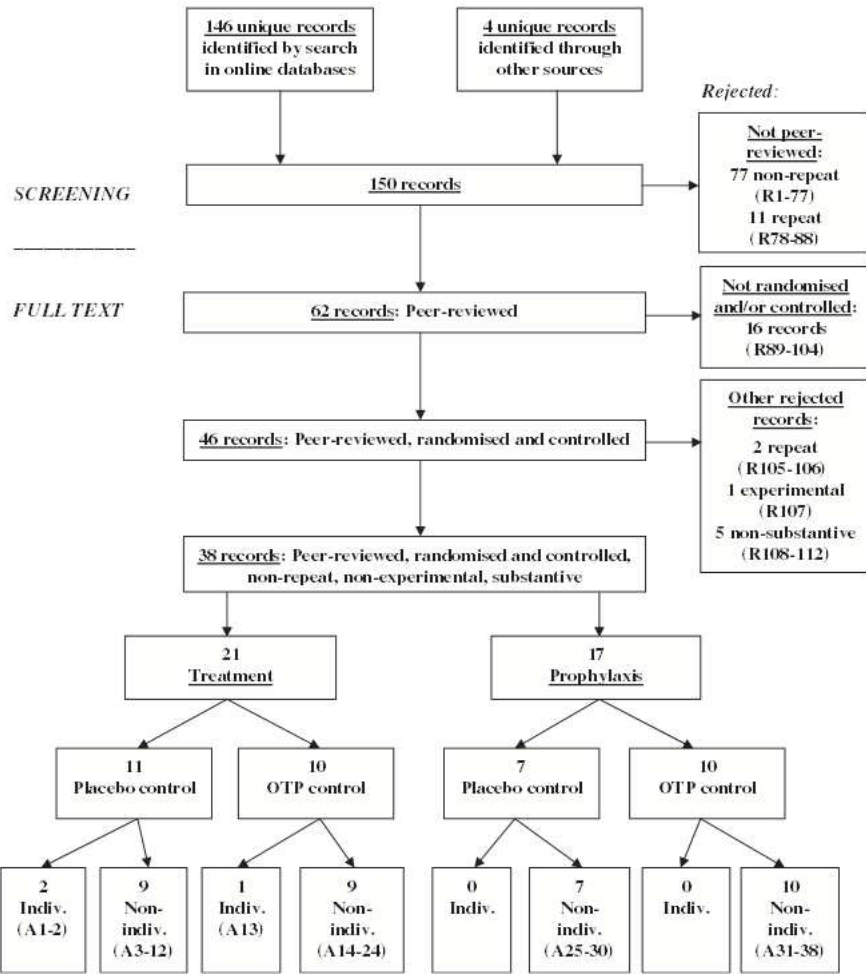


Figure 1 PRISMA flowchart: inclusion and exclusion of records reporting RCTs in veterinary homeopathy. See also Web Appendix and Table 1. Key to abbreviations: OTP = other than placebo; Indiv. = individualised homeopathy.

- Language used in main text;
- Treatment or prophylaxis;
- Placebo control or OTP control;
- Individualised homeopathy or non-individualised homeopathy.

At this initial stage, a paper reporting >1 RCT is listed once only and is identified, as appropriate, solely by the first-named of each of the following attributes: treatment or prophylaxis; placebo control or OTP control.

Similarly, a paper reporting a single RCT comprising >2 groups of animals is listed once only at this stage, and identified (prioritised for identification as above) by the attributes of just one pair of groups.

Results: literature search findings

One hundred and fifty unique records were identified as potentially eligible for systematic review (PRISMA flowchart: Figure 1).

Records rejected from further analysis

Of the 150 records, 88 lie in the non-peer-reviewed literature. Eleven of those 88 records turned out to be a repeat publication of an identical study that is elsewhere in our lists, and so 77 are unique records of non-peer-reviewed research.

Amongst these 77 unique non-peer-reviewed records the largest category is research thesis ($n = 39$). Each of the non-peer-reviewed records was retrieved typically from a single electronic database (*HomVetCR* or *Hom-Inform*); German is the majority language in these publications ($n = 47$). The peak period of publication has been 1986–1990 (Figure 2); the median year of publication is 1992.

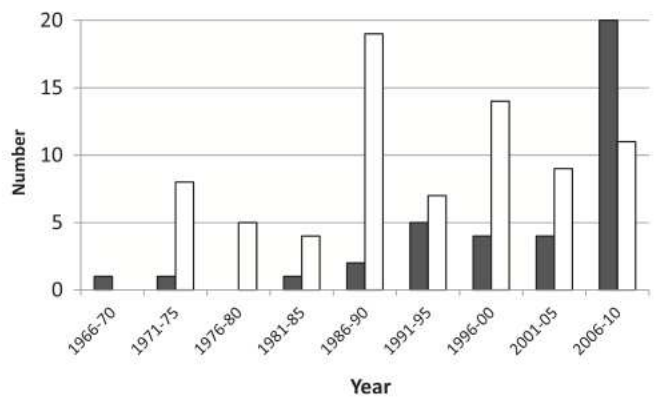


Figure 2 Number of records published per 5-year period. Filled bars: peer-reviewed records (total of 38 records). Unfilled bars: non-peer-reviewed records (total of 77 records).

Closer inspection of the 62 remaining (i.e. peer-reviewed) records revealed that the study design was not in fact randomised and/or controlled in 16 cases. Eight other peer-reviewed records were excluded from further assessment: 2 repeat publications, 1 experimental study, and 5 non-substantive papers. None of the remaining 38 papers was ineligible on the basis of 'homeopathic' formulation. Thus, a total of 112 records were rejected from further analysis (see Web Appendix for details).

Records accepted for further analysis

Table 1 comprises the 38 substantive peer-reviewed articles that satisfied our eligibility criteria for acceptance and have thus been identified for full data extraction (and presentation of quality assessment) in subsequent reports. Each of these records was retrieved from a median of 2 electronic databases (interquartile range, 1–3 databases). The online databases yielded a widely varying number of these 38 records: total retrieval numbers ranged from 37 of 38 (*HomVetCR*) and 15 of 38 (*PubMed*) to 3 of 38 (*AMED* and *CINAHL*). The most common language of publication is English ($n=29$), followed by German ($n=8$) and Portuguese ($n=1$). The peak period of publication has been 2006–2010 (Figure 2); the median year of publication is 2006.

There are 7 species (avian, bovine, canine, caprine, equine, ovine, porcine) and a total of 27 different species-specific medical conditions represented in the 38 accepted peer-reviewed papers. There are just 6 species-specific conditions in which more than a single RCT has been carried out: anoestrus, cattle tick, diarrhoea and mastitis (bovine); diarrhoea (porcine); weight gain (avian). The number of papers per species varies from 18 (bovine) and 8 (porcine) to 2 (equine and ovine) and 1 (caprine). The total number of reports of research on livestock animals (including chickens) comprises 32 of the 38 papers; the remaining 6 papers have reported findings in dogs or horses.

Of the 38 peer-reviewed records, treatment trials ($n=21$) have been reported with similar frequency as prophylaxis trials ($n=17$) – see Figure 1 and Table 1. There are also similar numbers of peer-reviewed papers that have reported placebo-controlled trials ($n=18$) and OTP trials ($n=20$). A large majority of this veterinary research has focused on non-individualised homeopathy ($n=35$) compared with individualised homeopathy ($n=3$).

Discussion

Our search findings and initial data extraction provide a greatly clarified view of the clinical trial literature in veterinary homeopathy, which has hitherto been incompletely identified. As intended, these findings offer new and important information about veterinary homeopathy, especially for those engaged in its research. Also as planned, our work has enabled us to identify the literature that we deem acceptable for full systematic review of RCTs in this field: the papers listed in Table 1 comprise the material for that consequent detailed assessment. At that later stage of the review process, we shall itemise the number of

papers reporting >1 RCT; we shall then complete the *PRISMA* flowchart to indicate the number of trials per category that will be subject to full systematic review.

After excluding 11 repeat records, we have identified 139 unique publications, which are split approximately equally between the peer-reviewed ($n=62$) and the non-peer-reviewed literature ($n=77$). Because of our current focus prospectively on the peer-reviewed literature only, we are not in a position to know how many of the 77 unique records in the non-peer-reviewed literature are truly randomised and/or controlled. In the peer-reviewed literature, 38 of the substantive and non-repeated papers were sufficiently randomised and/or controlled to be acceptable for consequent detailed review.

Compared to the non-peer-reviewed records, the accepted peer-reviewed literature has greater emphasis on English-language and recent publications, each of which was retrieved typically from a larger number of databases than the non-peer-reviewed records. With their low rate of record retrieval (e.g. 15 of the 38 accepted peer-reviewed papers found in *PubMed*), it is clear that the normally used bibliographic databases are unsuitable for reliably identifying RCTs in veterinary homeopathy, and that specialist resources such as *HomVetCR* (Carstens Foundation) are an essential source of information. *HomVetCR* failed to identify just 16 out of the grand total of 150 records [data not shown]; this database now comprises, or has re-categorised, each of those 16 records. The high rates of non-English and of specialised articles in homeopathy and/or veterinary medicine are probably the main reasons for the relative failure of standard databases to identify many peer-reviewed records in our field of research interest. If the rapid increase in peer-reviewed papers in the recent international literature is sustained into a new decade, there may be hope that the proportion of easily retrievable articles from the main databases will increase correspondingly.

As previously advocated by others,¹⁹ it is appropriate that trials published outside the peer-reviewed journal literature have not been accepted for appraisal in this programme of systematic reviews. Despite some intrinsic flaws, the peer-review process undoubtedly raises the standard of published research, and prominent authorities see little or no worth in science that is disseminated outside this domain.²⁰ In those non-peer-reviewed records that we had occasion to read in the current work, it was invariably the case that the quality and clarity of the research were of perceptibly low standard. Nevertheless, we recognise that such research should not be dismissed entirely, and it is our intention later in the future to appraise this literature more fully.

Our categorisation approach enabled us to identify and accept 21 peer-reviewed records of treatment trials and 17 of prophylaxis trials. Attributing the 'correct' category per paper was not always straightforward: this problem was generally caused by the original paper's lack of clarity in whether or not the trial had been carried out on disease-free animals. A final decision on each such paper was readily achieved by consensus discussion amongst our own three-author group, and we are satisfied that the categorisations represent a reasonable reflection of the literature. For

Table 1 Records accepted for further analysis

<i>Ref. no.</i>	<i>First author</i>	<i>Year</i>	<i>Databases</i>	<i>Lang.</i>	<i>Indiv.</i>	<i>Species</i>
(a) Veterinary homeopathic treatment (<i>n</i> = 21)						
(i) Controlled by placebo						
A1	Hektoen	2004	4	Eng.	Yes	Bovine (cow)
A2	Werner	2010	2	Eng.	Yes	Bovine (cow)
A3	Andersson	1997	2	Ger.	No	Bovine (cow)
A4	Cracknell	2008	4	Eng.	No	Canine
A5	de Verdier	2003	4	Eng.	No	Bovine (calf)
A6	Fidelak	2007	5	Ger.	No	Bovine (cow)
A7	Hielm-Björkman	2009	3	Eng.	No	Canine
A8	Holmes	2005	2	Eng.	No	Bovine (cow)
A9	Kayne	1994	2	Eng.	No	Bovine (calf)
A10	Searcy	1995	3	Eng.	No	Bovine (cow)
A11	Wolter	1966	1	Ger.	No	Porcine (sow)
(ii) Controlled by other than placebo						
A12	Schütte	1988	1	Ger.	Yes	Porcine (sow)
A13	Beceriklisoy	2008	1	Eng.	No	Canine
A14	Coelho	2009	1	Eng.	No	Porcine
A15	Faulstich	2006	2	Ger.	No	Equine (horse)
A16	Klocke	2010	5	Eng.	No	Bovine (cow)
A17	Rocha	2006	1	Eng.	No	Ovine (sheep)
A18	Sandoval	1998	1	Eng.	No	Avian (chicken)
A19	Silva	2008	1	Eng.	No	Bovine (heifer)
A20	Varshney	2005	1	Eng.	No	Bovine (cow)
A21	Zacharias	2008	3	Eng.	No	Ovine (lamb)
(b) Veterinary homeopathic prophylaxis (<i>n</i> = 17)						
(i) Controlled by placebo						
A22	Albrecht	1999	4	Eng.	No	Porcine
A23	Arit	2009	4	Eng.	No	Bovine (cow)
A24	Camerlink	2010	4	Eng.	No	Porcine (piglet)
A25	Danieli	2009	1	Eng.	No	Caprine (kid)
A26	Guajardo-Bernal	1996	2	Eng.	No	Porcine
A27	Soto	2010	1	Eng.	No	Porcine (sow)
A28	Williamson	1995	3	Eng.	No	Bovine (cow)
(ii) Controlled by other than placebo						
A29	Dreismann	2010	0	Ger.	No	Equine (foal)
A30	Lepple	1984	1	Ger.	No	Canine
A31	Reis	2006	2	Eng.	No	Bovine (calf)
A32	Reis	2008	1	Eng.	No	Bovine (calf)
A33	Sharma	1987	1	Eng.	No	Avian (chicken)
A34	Signoretti	2008	2	Por.	No	Bovine
A35	Sommer	1972	1	Ger.	No	Bovine (cow)
A36	Soto	2008	5	Eng.	No	Porcine (piglet)
A37	Trehan	1994	1	Eng.	No	Avian (chicken)
A38	Williamson	1991	2	Eng.	No	Bovine (cow)

Key to abbreviations: Ref. no. = Reference number; Indiv. = Individualised homeopathy; Eng. = English; Ger. = German; Por. = Portuguese.

Table 1 (cont.): References

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example, all trials on bovine mastitis are grouped together under the heading 'treatment' and all trials on 'performance (weight gain)' are classified as 'prophylaxis'.

There are almost equal numbers of placebo-controlled trials and OTP trials. A large majority of this research has studied non-individualised homeopathy, and it is striking that there are only three RCTs of individualised homeopathy in the entire accepted literature. This is a reflection of the large proportion of RCTs that has involved livestock animals, in which the homeopathic intervention has generally been a single remedy selection for an entire herd or flock rather than individualised (constitutional) prescribing. It is noteworthy how few homeopathy RCTs have been reported on dogs and horses, as is the total absence of any peer-reviewed research on cats. This is remarkable because cats, dogs and horses are often subject to homeopathy treatment, as can be inferred from recent clinical outcomes studies in veterinary homeopathy.^{4–6} In addition to the difficulty of recruiting sufficient numbers of non-herd animals, the paucity of RCTs in companion animals may be a consequence of the individualised homeopathic approach they generally require and thus the time involved in repertorising each patient's symptoms indirectly via interview with its owner.

The heterogeneity of the acceptable peer-reviewed research (38 papers), comprising seven species and 27 species-specific medical conditions, brings a substantial challenge to data analysis, synthesis and reporting; a comprehensive or condition-specific meta-analysis will thus not be prioritised. Our consequent systematic reviews of this literature will focus mainly on the *qualitative* appraisal of internal validity (risk of bias) and outcome measures of the research. The findings of the full data extraction and assessment of this complex literature will be carried out systematically under two main headings: treatment trials; prophylaxis trials.

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Supplementary data: Web Appendix

Supplementary data related to this article (Web Appendix) can be found at <http://dx.doi.org/10.1016/j.homp.2012.05.009>.

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