Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes (Review)

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2006, Issue 3

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[Intervention Review]

Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: Unchanged, commented, published in Issue 2, 2009.
Review content assessed as up-to-date: 19 May 2006.

Citation: Vickers A, Smith C. Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD001957. DOI: 10.1002/14651858.CD001957.pub3.

ABSTRACT

Background

Influenza is a highly infectious viral disease that is particularly common in the winter months. Oscillococcinum is a patented, commercially available homoeopathic medicine. The rationale for its use in influenza comes from the homoeopathic principle of 'let like be cured by like'. This medicine is manufactured from wild duck heart and liver, which are said to be reservoirs for influenza viruses.

Objectives

To determine whether homoeopathic Oscillococcinum or similar medicines are more effective than placebo in the prevention and treatment of influenza and influenza-like syndromes.

Search strategy

We updated the electronic searches on the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2006); MEDLINE (January 1966 to February 2006) and EMBASE (1980 to February 2006). The manufacturers of Oscillococcinum were contacted for information.

Selection criteria

Placebo-controlled trials of Oscillococcinum or homeopathically-prepared influenza virus, influenza vaccine or avian liver in the prevention and treatment of influenza and influenza-like syndromes.

Data collection and analysis

Two authors extracted data and assessed methodological quality independently.

Main results

Seven studies were included in the review, three prevention trials (number of participants (n) = 2265) and four treatment trials (n = 1194). Only two studies reported sufficient information to complete data extraction fully. There was no evidence that homoeopathic treatment can prevent influenza-like syndrome (relative risk (RR) 0.64, 95% confidence interval (CI) 0.28 to 1.43). Oscillococcinum treatment reduced the length of influenza illness by 0.28 days (95% CI 0.50 to 0.06). Oscillococcinum also increased the chances that a patient considered treatment to be effective (RR 1.08; 95% CI 1.17 to 1.00).

Authors' conclusions

Though promising, the data were not strong enough to make a general recommendation to use Oscillococcinum for first-line treatment of influenza and influenza-like syndromes. Further research is warranted but the required sample sizes are large. Current evidence does not support a preventative effect of Oscillococcinum-like homeopathic medicines in influenza and influenza-like syndromes.

PLAIN LANGUAGE SUMMARY

Homoeopathic Oscillococcinum does not prevent influenza but might shorten the length of the illness

Influenza (the flu) is a highly infectious respiratory disease caused by viruses. Other than treatments for complications (such as pneumonia) conventional medical treatment is bed rest. Homeopathy is a system based on 'curing like with like', often using highly diluted substances. Oscillococcinum is a homoeopathic preparation manufactured from wild duck heart and liver (common sources of influenza). It is claimed that Oscillococcinum (or similar homeopathic medicines) can be taken either regularly over the winter months to prevent influenza or as a treatment. Trials do not show that homoeopathic Oscillococcinum can prevent influenza. However, taking homoeopathic Oscillococcinum once you have influenza might shorten the illness, but more research is needed.

BACKGROUND

Influenza is a highly infectious viral disease that is particularly common in the winter months. Though several prescription-only agents can prevent or reduce the duration of influenza, much influenza is treated in the community without the involvement of a physician. Oscillococcinum is a patented homeopathic medicine that is commercially available over the counter. The rationale for its use in influenza comes from the homeopathic principle of 'let like be cured by like'. The medicine is manufactured from wild duck heart and liver, which are said to be reservoirs for influenza viruses.

The homeopathic method of preparation is known as 'Korsakov potentisation'. An extract of the liver and heart is prepared, shaken in a test tube and then poured off. A hydroalcoholic solution is added to the test tube to dilute the drops remaining on the sides of the glass. This is again shaken and poured off and the process repeated a total of 200 times. The resulting medicine is so dilute that a typical dose does not contain even a single molecule of the active ingredient (Kayne 1997). Though this no doubt improves the safety profile of homeopathic medicines, high dilution raises serious questions about the plausibility of homeopathy: how can a medicine work if the active ingredient is diluted away?

Despite its implausibility, Oscillococcinum is widely utilised; it is one of the best selling over-the-counter medicines in France. The commercial success of Oscillococcinum has spawned a number of homeopathic medicines produced from similar material but in a slightly different manner. These are used by over 1000 UK physicians and 10,000 French and German homeopathic physicians (UKFoH 1999).

This present study reviewed randomised controlled trials (RCTs) of Oscillococcinum-type medicines for the prevention and treatment of influenza and influenza-like syndromes. Influenza-like syndromes will be defined here as symptoms of influenza, such as cough, fever, chills and muscle pain, in the absence of laboratory evidence of infection.

The review may shed light on the more general question of whether homeopathic medicines are always equivalent to placebo. In a meta-analysis of all placebo-controlled trials of homeopathy, Linde (Linde 1997) found statistically significant differences between groups. However, no set of trials met Linde's criteria for reproducibility: at least three different investigators studying the same clinical condition, the same treatment or treatment model with a similar population and outcome measure. It may be that the Oscillococcinum data constitute such a set of reproduced studies.

OBJECTIVES

To determine whether homeopathic Oscillococcinum, or similar medicines, are more effective than placebo in the prevention and treatment of influenza and influenza-like syndromes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) with placebo control.

Types of participants

Patients wishing to prevent or presenting with influenza or influenza-like syndromes (symptoms of influenza, such as cough, fever, chills and muscle pain, in the absence of laboratory evidence of infection).

Types of interventions

Homeopathically-prepared Oscillococcinum in any frequency or dose. Medicines made from homeopathically-prepared influenza virus, influenza vaccine or avian liver were also included.

Types of outcome measures

Any measure of influenza severity or duration except laboratory findings (for example, antibody titres).

Search methods for identification of studies

In 1999, the registry of randomised trials for the Complementary Medicine Field of The Cochrane Collaboration was searched using the terms "homeopathy" with "influenza", "respiratory tract", "infection", "cough", "virus" and "fever". This registry had then recently benefited from incorporating trials found during an extremely comprehensive systematic review of homeopathy (Linde 1997) and it was considered unlikely that further studies existed. Homeopathic manufacturers were contacted for information about other trials.

For the first update of this review, published in Issue 1, 2004, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2003); MEDLINE (January 1966 to June 2003); and EMBASE (1980 to June 2003) but no new trials were found. There were no language restrictions.

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2006); MEDLINE (January 1966 to February 2006) and EMBASE (1980 to February 2006). The manufacturers of Oscillococcinum were contacted for information. There were no language restrictions.

MEDLINE (OVID)
#1. exp HOMEOPATHY/
#2. homeopath$.mp.
#3. homoeopath$.mp.
#4. oscillococcinum.mp.
#5. or/1-4
#6. exp INFLUENZA/
#7. influenza.mp.
#8. flu.mp.
#9. exp COUGH/
#10. cough$.mp.
#11. exp VIRUSES/
#12. virus$.mp.
#13. exp Respiratory Tract Infections/
#14. exp Respiratory System/
#15. respiratory tract$.mp.
#16. exp INFECTION/
17. infection$.mp.
18. exp FEVER/
19. fever$.mp.
20. or/6-19
21. 5 and 20
22. limit 21 to yr=2003-2006

Data collection and analysis

Inclusion criteria were applied by two reviewers working independently. There were no disagreements about study inclusion.

The following data on the trial participants were extracted from included trials: inclusion and exclusion criteria; and method and place of recruitment (for example, primary care). The following data on trial participants were extracted separately by group: number randomised; number of withdrawals; age; and sex. For each outcome measure, the number of participants and mean and standard deviation (SD) or number of events were recorded by group. Ordinal scales were turned into binomial variables by treating each participant as 'improved' or 'not improved'. Data on time to absence of symptoms were converted, where necessary, from numbers of patients who were symptom free at each follow up to a mean and standard deviation (SD). For these calculations participants not recovering during the study were assumed to have recovered on the following day. If continuous variables (such as pain or temperature) were reported at more than one follow up the results for the second day (or evening thereof) were taken. Details of the treatment given and adverse events reported for the experimental and comparison groups were recorded. Data collection forms were completed by each author independently. Attempts were made to contact trial authors to clarify or provide missing data. Manufacturers were contacted for trial reports. Disagreements between review authors were resolved by consensus.

The methodological criteria used to appraise each paper were: concealment of treatment allocation (was treatment allocation concealed until the patient had been unambiguously entered into the trial? could it have been altered after entry?); performance bias (were patients treated similarly in all respects other than the experimental intervention?); blinding of observers (were those assessing outcome blind to treatment assignment?); and exclusions and withdrawals (were there systematic differences in withdrawals

from the trial?). Each criterion was graded A, B or C: A indicated a low risk of bias, where the plausibly postulated bias was unlikely to alter the results seriously; C, on the other hand, indicated a high risk of bias, where plausibly postulated bias seriously weakened confidence in the results; a criterion was graded B if it was partially met or where no data were available such that some doubt was raised about possible bias. Each paper was graded independently by both authors with disagreements resolved by discussion.

Standard statistical packages provided by The Cochrane Collaboration were used to analyse data. A grade of C on concealment of treatment allocation was grounds for excluding the trial from the review. All other trials were included. It was planned to analyse treatment and prevention trials separately. A planned subgroup analysis was to analyse trials of patented Oscillococcinum (Boiron) separately.

Two methods of data analysis were unplanned at the protocol stage. The data for individual symptoms for Casanova 1984 and Casanova 1992 were dichotomous. For Papp 1998 however, these data were recorded on an ordinal scale (no symptoms, mild, moderate, severe) and presented as means and SDs. As any particular mean and SD can correspond to various distributions of ordinal data, a simulation was conducted for each outcome by group in order to convert these data into dichotomous variables. Firstly, a hypothetical set of patients was assigned at random to have reported one of the ordinal outcomes. A mean and SD were then calculated using the same method as Papp (Papp 1998). Next, the number of patients assigned to each ordinal outcome was adjusted to bring the mean and SD closer to the reported value. This process was iterated until the mean and SD of the simulated data came close to the trial data. The number of patients reporting no symptoms was then recorded. One hundred simulations were conducted for each outcome for each group. The results were averaged to produce the values used in the review.

A second unplanned method of data analysis used was the conversion of continuous data on temperature to the dichotomous outcome of fever, using the assumption that the data were normally distributed. Fever was defined as temperature greater than 37.7 ^{0}Celsius. A z value was calculated by taking the mean temperature from 37.7 ^{0}Celsius and dividing by the SD. The z value was converted to a proportion using STATA for Macintosh (Stata Corporation, Texas 77840, USA).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Seven studies were included in this review: four treatment trials (Casanova 1984; Casanova 1992; Ferley 1989; Papp 1998) with a total number of participants of 1194; and three prevention trials (Attena 1995; Nollevaux 1990; Rottey 1995), total number of participants of 2265. All the treatment trials compared patented Oscillococcinum (Boiron) to placebo. Two of the prevention trials (Nollevaux 1990; Rottey 1995) used homeopathically-prepared mixtures of inactivated bacteria and influenza viruses. The third prevention trial (Attena 1995) used extract of heart and liver of wild duck (similar to that used in the preparation of Oscillococcinum) in a 200 C potency (that is, diluted 1 in 100 repeated 200 times).

Four studies (Attena 1995; Ferley 1989; Nollevaux 1990; Papp 1998) reported outcomes that depended on the presence or absence of influenza-like syndrome. Patient assessment of treatment success was reported in three studies (Casanova 1984; Ferley 1989; Papp 1998). In one study (Rottey 1995) physicians assessed the effectiveness of treatment on an 11-point scale. Use of concomitant medication was reported in two trials (Ferley 1989; Papp 1998). Five trials (Casanova 1984; Casanova 1992; Nollevaux 1990; Papp 1998; Rottey 1995) reported outcomes for individual symptoms of influenza, such as fever, chills, aches or cough. Only one of the treatment studies (Ferley 1989) explicitly reported that patients were accrued during an outbreak of influenza.

Patients were generally recruited from primary care settings. Most trials included both children and adults. Inclusion and exclusion criteria were often not described. In two of the four treatment trials, patients had to meet a defined standard for influenza-like syndrome (for example, rectal temperature more than 38 ^{o}Celsius and at least two episodes of headache, stiffness, lumbar and articular pain or shivers). Exclusion criteria in these two trials included duration of symptoms greater than 24 hours, immune deficiency, influenza vaccination or immunostimulant treatment.

Full details are given in the table Characteristics of included studies.

Risk of bias in included studies

The standard of trial reporting was poor. For only two studies was there sufficient information to complete data extraction fully (Ferley 1989; Papp 1998). Two trials (Casanova 1992; Nollevaux 1990) were unpublished; a third (Casanova 1984) was reported in a general medical magazine rather than in a scientific journal. Accordingly, this paper was reported very briefly and most important experimental details were missing. No details of exclusions and withdrawals were given in three papers (Casanova 1984; Casanova 1992; Rottey 1995). The sample sizes in the two Casanova papers are suspiciously round numbers (100 and 300).

The methodological bias in this set of trials is likely to be moderate. Except for Nollevaux (Nollevaux 1990), all were multi-centre studies in which it appears that blinded medication was provided to physicians for the trial participants. Homeopathic medicines

are generally impossible to distinguish from their placebo because they are white and have no inherent taste, smell or obvious adverse effects such as dry mouth. As such, it is difficult to see how bias could have been introduced during the trials themselves. More likely is bias at the stage of reporting and data analysis. At least one paper (Rottey 1995) described outcomes in the methods section for which no data were presented in the results. In another case, one author conducted two trials (Casanova 1984; Casanova 1992). The first of these trials reported data for patient assessment, chills, aches, rhinitis, night cough, day cough and fever. The second trial reported data only for temperature, chills and aches. Were data on rhinitis, cough and patient assessment recorded but not reported? Moreover, the length of follow up varied between the two trials: the first reported data for day eight; the second for day four. Could it have been that data were recorded daily but only the most favourable comparisons reported? Given these considerations the outcomes for individual symptoms are more likely to be biased than those for presence or absence of influenza or use of concomitant medication. A sensitivity analysis was conducted to control for reporting bias with patient assessment (see Results).

Effects of interventions

Prevention trials

Influenza outcome

There was heterogeneity between trials (chi squared = 6.5; P = 0.01) for the occurrence of influenza-like syndromes. Using a random-effects model, the relative risk (RR) of influenza-like syndromes in those receiving treatment was 0.64 (95% CI 0.28 to 1.43). Though this is not statistically significant the 95% CI does include values of clinical relevance.

Physician assessment

Physician assessment was reported only in Rottey (Rottey 1995). Participants receiving treatment had a 1.06 point higher assessment than controls. The 95% CI (0.56 to 1.51) does not include zero difference between groups but may not be reliable because the data were not normally distributed.

Symptoms

Only Rottey (Rottey 1995) reported individual symptom scores. Though all reached statistical significance, there were concerns about selective reporting. There was no statistically significant difference between groups for total number of symptoms (0.35 fewer symptoms in treated group, 95% CI -0.07 to 0.77).

Adverse events

Attena (Attena 1995) reported a very much higher rate of adverse events in the active group. Seventy-seven out of 783 (9.83%) participants who received homeopathy reported side-effects compared to 17 of 790 (2.15%) on placebo. A Pearson two-tailed chi-squared analysis gives chi-squared at 41.3, equivalent to the extremely small P value of 1.3×10^{-10}.

Treatment trials

Influenza outcome

Two trials (Ferley 1989; Papp 1998) pre-specified 'recovery after 48 hours' as the main outcome measure. The RR of being sick at 48 hours on Oscillococcinum was 93% (95% CI 88% to 99%) of that of placebo (event rate 87%), corresponding to a number needed to treat to benefit (NNT) of 17 (95% CI 9 to 111). The number of days to recovery was reduced by 0.26 (95% CI 0.47 to 0.05) from a control mean of 4.9 days. Number of days to return to work was also reduced by 0.49 days (95% CI 0.89 to 0.08) from a control mean of 4.1. One outcome was only reported by Papp (Papp 1998); patients taking Oscillococcinum approximately halved their chance of experiencing no improvement after 48 hours (0.47; 95% CI 0.29 to 0.75) with an NNT of 8 (95% CI 5 to 20).

Patient assessment

There was heterogeneity between trials for patient assessment (chi squared = 7.26; P = 0.03). Using a random-effects model, Oscillococcinum increased the chance of a patient considering the treatment effective by 40% (95% CI 63% to 2%), NNT of 6 (95% CI 3 to 100). As data on patient assessment were reported by Casanova in 1984 (Casanova 1984) but not 1992, a sensitivity analysis was conducted. It was assumed that in Casanova (Casanova 1992) the event rate in both groups for 'treatment not a success' was the same as that reported for the control group in Casanova (Casanova 1984). Heterogeneity between trials was still significant (chi squared = 14.58; P = 0.002) and so a random-effects model was used. The RR was 0.75 (95% 0.52 to 1.03), which is not appreciably different from the original analysis. An approach that required fewer assumptions was to remove Casanova (Casanova 1984). A meta-analysis of Ferley (Ferley 1989) and Papp (Papp 1998) had no evidence of heterogeneity: RR is 0.75 (95% CI 0.58 to 0.99; NNT 16, 95% CI 8 to 333).

Concomitant medication

Medication use was lower on Oscillococcinum, though only one comparison reached statistical significance; Ferley (Ferley 1989) reported an 18% (95% CI 33% to 0%) lower use of analgesics and antipyretics.

Symptoms

Most analyses of individual symptoms favour homeopathy, though not all reach statistical significance. A particularly interesting result was that Oscillococcinum reduced temperature by 0.38 ^{o}Celsius (95% CI 0.15 to 0.62).

Adverse events

Most trials did not describe a pre-defined method for assessment of adverse events. One patient taking Oscillococcinum in Papp (Papp 1998) reported a headache that was deemed 'possibly' due to the trial medication. Ferley reported a 3.2% overall rate of adverse events with no difference between groups. No serious adverse events appear to have been reported for the medication elsewhere in the literature.

DISCUSSION

Current evidence does not support a preventative effect of homeopathy in influenza and influenza-like syndromes. Probably the main question to be answered is whether further research is warranted. The central estimate of effect size in the meta-analysis is of clinical relevance and it may be that the lack of statistical significance is due to insufficient power. Even if the positive results of Nollevaux (Nollevaux 1990) are excluded from the analysis on grounds of insufficient methodological rigour, the confidence intervals of Attena (Attena 1995) alone include differences between groups that are of clinical value.

There is some evidence that prophylactic use of homeopathy may lead to adverse events (Attena 1995). The reported effects were mild (for example, headache) and transient, and might be described by homeopaths as a 'proving' phenomenon. This is when a medicine causes the symptoms in a healthy person that it cures in the sick. Casting doubt on this effect, however, is that no assessment of adverse events was planned (Attena 1999) and that similar data were not reported for the other two prevention trials. Nonetheless, the possibility of adverse events, however mild or transient, does suggest caution especially given the lack of strong evidence of benefit.

Oscillococcinum appears to have a moderate effect in the treatment of influenza and influenza-like syndrome. Participants taking Oscillococcinum had about a quarter of a day less illness than those on placebo. This effect might be as large as half a day and as small as about an hour. Return to work was about a half day earlier. Patient satisfaction was greater on Oscillococcinum: approximately 12 patients need to be treated to prevent one believing that treatment was not a success. Although there were insufficient data to determine the effect of Oscillococcinum on concomitant medication, one trial reported a decreased use of antipyretic and analgesic medication. There were insufficient data to judge either the effects of Oscillococcinum on those especially vulnerable to influenza, such as elderly people, or the relative effects of different doses of Oscillococcinum. Though Ferley (Ferley 1989) reported a better response to treatment in people aged less than 30 years, this finding was based on an unplanned subgroup analysis.

The data for patient assessment of success do meet the Linde criteria for a set of reproduced studies in homeopathy. Nonetheless, doubts remain. The main difficulty is that one of the trials, Casanova (Casanova 1984), was not published in a standard medical journal, contains little experimental detail, does not report withdrawals and analyses a suspiciously round number of patients. Moreover, the difference between groups in the meta-analysis only just reaches statistical significance. It is arguable that a question as scientifically controversial as whether homeopathic medicines are always equivalent to placebo would require more statistically robust data.

AUTHORS' CONCLUSIONS

Implications for practice

Though promising, the evidence was not strong enough to make a general recommendation to use Oscillococcinum for routine treatment. The data do not support the use of Oscillococcinum-like homeopathic medicines to prevent influenza and influenza-like syndromes.

Implications for research

Confirmatory trials of Oscillococcinum as a treatment are warranted. The main difficulty of such trials will be the requirement for a large sample size. Oscillococcinum is inexpensive (approximately $5 US per influenza episode), easy to take and apparently very safe. It is worth taking Oscillococcinum even if it is of only very moderate benefit. At a population level, there would be significant social gains from even a five per cent reduction in the length of influenza episodes.

However, detecting such moderate but worthwhile benefits would require large sample sizes. A sample size calculation was conducted for time to recovery using the pooled mean (4.61) and SD (1.73) from the control arms of Ferley (Ferley 1989) and Papp (Papp 1998). The minimal, clinically significant difference was assumed to be a quarter of a day (though even smaller differences might be considered worthwhile) and power set at 90%. The required sample is 2000. A similar figure (2200) was determined using recovery in 48 hours as the main outcome measure and an absolute difference of 5% as the minimal difference. A trial measuring time to return to work in which control patients had similar results to those in Papp (Papp 1998) (mean 5.29 days; SD 2.7) would require 4904 patients in total to detect a difference of a quarter

of a day with 90% power. A similar number of patients (4270) would be needed for a trial attempting to detect a 10% decrease in use of antipyretic and analgesic medication (the rate in controls in Ferley (Ferley 1989) was 50%). A 10% decrease in the use of antibiotics, a similar rate to that found by Ferley 1989 and a fall of social value at the population level would require nearly 50,000 patients. Future trials of Oscillococcinum should plan subgroup analyses to investigate Ferley's finding of a much stronger effect of treatment in patients under 30 years of age.

It is open to debate whether further research is warranted on homeopathic medicines to prevent influenza and influenza-like syndromes. Using the control event rate from the meta-analysis of Attena (Attena 1995) and Nollevaux (Nollevaux 1990) (24%), a minimal, clinically significant difference of 5%, and a power of 90% gives 1457 patients per group. Such a trial would require significant resources, the investment of which is questionable given the equivocal nature of the current data.

ACKNOWLEDGEMENTS

Robbert van Haselen, Sylvia Breugem and Caroline Batzdorf provided translations. The authors wish to thank the following people for commenting on the draft of this updated review: Roy Buffery, Ville Peltola, Kuldeep Kumar and Cheryl Flynn.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Attena 1995

Methods	Treatment allocation: A Performance bias: A Observer blinding: A Exclusions/withdrawals: A
Participants	1595 outpatients. No details given for inclusion and exclusion criteria. No details of age or sex
Interventions	Extract of duck heart and liver 200 c, once a week for three weeks and then once one month later
Outcomes	At least one episode of influenza-like syndrome defined as temperature more than 37.7 Celsius and two episodes of chills, cough, myalgia, rhinitis or sore throat
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Casanova 1984

Methods	Treatment allocation: B Performance bias: B Observer blinding: B Exclusions/withdrawals: B
Participants	100 patients with influenza-like syndrome onset less then 48 hours previously. No details of method of recruitment or exclusion criteria. Average age verum/placebo: 42/41 years. Male:female in verum/placebo: 19:31/26:24
Interventions	Oscillococcinum, four doses in over two days at six-hour intervals
Outcomes	Patient global assessment of success; presence of chills, aches rhinitis, night cough, day cough, fever at day eight
Notes	Reported in what appears to be a general medical magazine: very few experimental details given

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Casanova 1992

Methods	Treatment allocation: B Performance bias: B Observer blinding: B Exclusions/withdrawals: B
Participants	300 patients complaining of influenza. No details of inclusion or exclusion criteria. Average age verum/placebo: 44/38. Male:female in verum/placebo: 61:89/56:94
Interventions	Oscillococcinum, twice a day for three to four days
Outcomes	Temperature recorded twice a day for four days (data for evening of second day used for continuous outcome, data for evening of day four converted to binomial outcome of fever, by using normal distribution) ; presence of chills, aches at day four
Notes	Inconsistency between text and table: the table appears to have been printed the wrong way around. The text value was selected

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ferley 1989

Methods	Treatment allocation: A Performance bias: A Observer blinding: A Exclusions/withdrawals: A
Participants	487 patients presenting in primary care with a complaint of influenza-like syndrome. Inclusion criteria: age older than 12 years; rectal temperature above 38 Celsius and at least two of headache, stiffness, lumbar and articular pain, shivers. Exclusion criteria: duration more than 24 hours; immune deficiency; local infection; immunisation against influenza; depression; immunostimulant treatment. Average age verum/placebo: 34/35. Male:female in verum/placebo: 93:127/97:129
Interventions	Oscillococcinum, twice a day for five doses
Outcomes	Patient assessment of success; recovery at 48 hours (defined as rectal temperature below 37.5 Celsius and complete resolution of all five symptoms); number of days to recovery; number of days to return to work; use of medication for pain or fever; use of medication for cough or sore throat; use of antibiotic medication; patient assessment of success
Notes	Use of medication calculated from percentages given in text. Some minor inconsistencies between figures suggest a small amount of missing data

Risk of bias

Ferley 1989 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Nollevaux 1990

Methods	Treatment allocation: B Performance bias: B Observer blinding: B Exclusions/withdrawals: B
Participants	200 participants recruited from students and staff of a nursing school. No inclusion criteria given. Exclusion criteria: conventional influenza vaccination, cortisone, anti-depressant medication, AIDS, lupus, collagen diseases. Age younger than 25/26 to 55/older than 55 in verum//placebo: 46/44/9//52/33/7
Interventions	A variety of inactivated viruses and bacteria prepared homoeopathically to a 200 K potency. One pill per fortnight for four months
Outcomes	Influenza, assessed at a 'control' consultation
Notes	Trial described as double-blind but not randomised

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Papp 1998

Methods	Treatment allocation: A Performance bias: A Observer blinding: A Exclusions/withdrawals: A
Participants	372 patients recruited in primary care or by internal medicine specialists. Inclusion criteria: rectal temperature above 38 Celsius; muscle pain or headache; one of shivering, cough, spinal pain, nasal irritation, malaise, thoracic pain, periarticular pain. Exclusion criteria: duration more than 24 hours; immune deficiency; local infection; immunisation against influenza; medical need for medication; immunostimulant or immunosuppressive treatment. Use of analgesics, antibiotics or anti-influenza agents in the first 48 hours was a post-randomisation exclusion criterion. Average age verum/placebo: 35/35. Male:female in verum/placebo: 95:93/96:88
Interventions	Oscillococcinum three times a day for three days

Papp 1998 (*Continued*)

Outcomes	Complete recovery after 48 hours; not improved after 48 hours; use of concomitant medication during trial; total symptoms score; time to recovery; time to return to work; patient assessment of success; temperature and presence of aches, headache, shivers, back or side pain, joint pain, spinal pain, cough, rhinitis, sore throat on evening of day two; fever calculated from temperature using normal distribution
Notes	Method of calculating proportions experiencing symptoms described in the text

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Rottey 1995

Methods	Treatment allocation: A Performance bias: A Observer blinding: A Exclusions/withdrawals: B
Participants	Patients of all ages recruited in general practice. 501 patients analysed: number randomised is not reported. No inclusion criteria given. Exclusion criteria: conventional influenza vaccination. Average age verum/ placebo: 39/37. Male:female for whole sample: 56%:44%
Interventions	A variety of inactivated viruses and bacteria prepared homoeopathically to a 200 K potency. One pill per week for 12 weeks
Outcomes	Number of flu symptoms (data non-normal); physician assessment (10 point scale; data non-normal); presence of fever, myalgia, headache, chills, rhinitis, otitis, "pneumopathies." No data reported for final four outcomes
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bungetzianu 1985	No evidence of randomisation, no clinical outcome measures
Ferley 1987	Not Oscillococcinum or an Oscillococcinum-type medicine
Heilmann 1992	Not Oscillococcinum or an Oscillococcinum-type medicine
Hourst 1982	Not Oscillococcinum or an Oscillococcinum-type medicine
Lecocq 1985	Not Oscillococcinum or an Oscillococcinum-type medicine
Lewith 1989	No clinical outcome measures
Masciello 1985	Not placebo controlled
Rabe 2004	Preparation does not contain homeopathically prepared influenza virus, influenza vaccine or avian liver

DATA AND ANALYSES

Comparison 1. Prevention: Oscillococcinum-like medicine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Occurrence of influenza-like syndrome	2	1764	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.28, 1.43]
2 Occurrence of adverse event	1	1573	Risk Ratio (M-H, Fixed, 95% CI)	4.57 [2.73, 7.65]
3 Number of symptoms	1	501	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.77, 0.07]
4 Physician assessment	1	501	Mean Difference (IV, Fixed, 95% CI)	1.06 [0.55, 1.57]
5 Fever	1	501	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.39, 0.91]
6 Myalgia	1	501	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.29, 0.87]
7 Headache	1	501	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.38, 1.06]

Comparison 2. Treatment: Oscillococcinum versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patient assessment: treatment not a success	3	852	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.37, 0.98]
2 Patient assessment sensitivity analysis	2	752	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.58, 0.99]
5 Not recovered at 48 hours	2	834	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.88, 0.99]
6 Not improved at 48 hours	1	372	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.29, 0.75]
10 Number of days to recovery	2	823	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.47, -0.05]
11 Number of days to return to work	2	742	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.89, -0.08]
20 Chills	3	715	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.41, 0.96]
21 Fever	3	714	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.08, 1.51]
22 Rhinitis	2	415	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.89, 1.09]
23 Sore throat	1	315	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.89, 1.10]
24 Aches	3	715	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.27, 1.36]
26 Headache	1	315	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.90, 1.05]
27 Back and side pain	1	315	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.78, 0.99]
28 Spinal pain	1	315	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.79, 1.06]
30 Cough	1	315	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.92, 1.14]
31 Night cough	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.47, 1.36]
32 Day cough	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.29, 0.93]
35 Total symptom score	1	315	Mean Difference (IV, Fixed, 95% CI)	-2.01 [-3.41, -0.61]
40 Temperature	2	614	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.52, -0.26]
50 Use of medication for pain or fever	1	462	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.67, 1.00]
51 Use of medication for cough or sore throat	1	462	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.76, 1.21]