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

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ABSTRACT

Background
Influenza is a highly infectious viral disease that is particularly common in the winter months. Conventional management options are limited to bed rest and treatment of complications such as secondary bacterial infections. 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'. The medicine is manufactured from wild duck heart and liver, a well-known reservoir 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
The registry of randomised trials for the Cochrane Complementary Medicine Field was searched in February 2001, using the term "homeopathy" with "influenza", "respiratory tract", "infection", "cough", "virus" and "fever". The manufacturers of Oscillococcinum were contacted for information about other trials. The Cochrane Acute Respiratory Infections Group's Register of Trials was also searched in March 2001, and no new trials were found.

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 reviewers extracted data and assessed methodological quality independently.

Main results
Seven studies were included in the review, three prevention trials (n=2265) and four treatment trials (n=1194). Only for two studies was there sufficient information to complete data extraction fully. There was no evidence that homoeopathic treatment can prevent influenza-like syndrome (relative risk 0.64, 95% confidence interval 0.28 to 1.43). Oscillococcinum treatment reduced length of influenza illness by 0.28 days (95% confidence interval 0.50 to 0.06). Oscillococcinum also increased the chance of a patient considering treatment effective (relative risk 1.08; 95% CI 1.17, 1).

Reviewer's conclusions
Oscillococcinum probably reduces the duration of illness in patients presenting with influenza symptoms. Though promising, the data are not strong enough to make a general recommendation to use Oscillococcinum for first-line treatment of influenza and influenza-like syndrome. Further research is warranted but required sample sizes are large. Current evidence does not support a preventative effect of homeopathy in influenza and influenza-like syndromes.

SYNOPSIS

Homoeopathic Oscillococcinum does not prevent influenza, but probably shortens the length of the illness

Influenza (the flu) is a highly infectious 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). Oscillococcinum can be taken regularly over the winter months to prevent flu, or as a treatment. The review found that trials do not show that it can prevent flu. Taking it once you have flu probably shortens the illness, but more research is needed.

BACKGROUND

Influenza is a highly infectious viral disease that is particularly common in the winter months. Conventional management options are limited to bed rest and treatment of complications such as secondary bacterial infections.

Oscillococcinum is a patented, commercially available ic medicine. 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, a well-known reservoir 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 then 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 in a slightly different manner. These are used by over 1000 UK, and 10,000 French and German, homeopathic physicians (Source: UK Faculty of Homeopathy).

This study will review randomised trials 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 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 and 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.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised trials with placebo control.

Types of participants

Patients presenting with, or wishing to prevent, 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 intervention

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 (e.g. antibody titres).

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: search strategy

The registry of randomised trials for the Complementary Medicine Field of the Cochrane Collaboration was searched using the term "homeopathy" with "influenza", "respiratory tract", "infection", "cough", "virus" and "fever". This registry recently benefited from incorporating trials found during an extremely comprehensive systematic review of homeopathy (Linde 1997) and it is unlikely that further studies exist. Homeopathic manufacturers were contacted for information about other trials. The most recent search of databases was conducted in February 2001. The Cochrane Acute Respiratory Infections Group's Register of Trials was also searched in March 2001, and no new trials were found.

METHODS OF THE REVIEW

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; method and place of recruitment (e.g. primary care). The following data on trial participants were extracted separately by group: number randomised; number of withdrawals; age; sex. For each outcome measure the number of participants and mean (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 symptom free at each follow-up to a mean and standard deviation. 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) are 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 reviewer independently. Attempts were made to contact authors to clarify or provide missing data. Manufacturers were contacted for trial reports. Disagreements between reviewers 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/withdrawals (were there systematic differences in withdrawals from the trial?). Each criterion was graded "A", "B" or "C": "A" indicates a low risk of bias, where the plausibly postulated bias is unlikely to alter the results seriously; "C", on the other hand, indicates a high risk of bias, where plausibly postulated bias seriously weakens confidence in the results; a criterion is graded "B" where it was partially met or where no data is available such that some doubt is raised about possible bias. Each paper was graded independently by both reviewers 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 sub-group analysis was to analyse trials of patented Oscillococcinum (Boiron).

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 standard deviations. As any particular mean and standard deviation 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 standard deviation were then calculated using the same method as Papp. Next, the number of patients assigned to each ordinal outcome was adjusted to bring the mean and standard deviation closer to the reported value. This process was iterated until the mean and standard deviation 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 was that continuous data on temperature were converted to the dichotomous outcome of fever using the assumption that the data were normally distributed. Fever was defined as temperature greater than 37.7 Celsius. A z value was calculated by taking the mean temperature from 37.7 and dividing by the standard deviation. The z value was converted to a proportion using STATA for Macintosh (Stata Corporation, Texas 77840, USA).

DESCRIPTION OF STUDIES

Seven studies were included in the review: four treatment trials (Casanova 1984, Casanova 1992, Ferley 1989, Papp 1998; total number of participants = 1194) and three prevention trials (Attena 1995, Nollevaux 1990, Rottey 1995; total number of participants = 2265). All the treatment trials compared patented Oscillococ-

cinum (Boiron) to placebo. Two of the prevention trials (Nollevaux 1990, Rottey 1995) used homeopathically-prepared mixtures of inactivated bacteria and influenza viruses. The third (Attena 1995) used extract of heart and liver of wild duck (similar to that used in the preparation of Oscillococcinum) in a 200C 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, Papp 1998, Nollevaux 1990, Rottey 1995) reported outcomes for individual symptoms of influenza, such as fever, chills, aches or cough.

Patients were generally recruited from primary care. 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 > 38 Celsius and at least two 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 of included studies.

METHODOLOGICAL QUALITY

The standard of trial reporting was poor. For only two studies was there sufficient information to complete data extraction fully (Papp 1998, Ferley 1989). 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 is reported very briefly and most important experimental details are 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).

That said, methodological bias in this set of trials is likely to be moderate. Except for Nollevaux 1990, all were multi-centre studies in which it appears that blinded medication was provided to physicians. homeopathic medicines are generally impossible to distinguish from their placebo because they are white, 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 reported data for patient assessment, chills, aches, rhinitis, night cough, day cough and fever; the second 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 these 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. To control for reporting bias for patient assessment, a sensitivity analysis was conducted (see Results).

RESULTS

Prevention trials

Influenza outcome

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

Physician assessment

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

Symptoms

Only Rottey 1995 reported individual symptom scores. Though all reached statistical significance, there are 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, 0.77).

Adverse events

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 x10^ -10.

Treatment trials

Influenza outcome

Two trials (Ferley, Papp) prespecified "recovery after 48 hours" as the main outcome measure. The relative risk of being sick at 48 hours on Oscillococcinum was 93% (95% CI 88%, 99%) of that of placebo (event rate 87%) corresponding to a "numbers-needed-to-treat" (NNT) of 17 (95% CI 9, 111). The number of days to recovery was reduced by 0.26 (95% CI 0.47, 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, 0.08) from a control mean of

4.1. One outcome was only reported by Papp: patients taking Oscillococcinum approximately halved their chance of experiencing no improvement after 48 hours (0.47; 95% CI 0.29, 0.75) with an NNT of 8 (95% CI 5, 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%, 2%), an NNT of 6 (95% CI 3, 100). As data on patient assessment were reported by Casanova in 1984, but not 1992, a sensitivity analysis was conducted. It was assumed that in 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 1984. Heterogeneity between trials was still significant (chi-squared = 14.58; P=0.002) and so a random effects model was used. The relative risk was 0.75 (95% 0.52, 1.03) which is not appreciably different from the original analysis. An approach that requires fewer assumptions is to remove Casanova 1984. A meta-analysis of Ferley 1989 and Papp 1998 has no evidence of heterogeneity: relative risk is 0.75 (95% CI 0.58,0.99; NNT 16, 95% CI 8, 333).

Concomitant medication

Medication use was lower on Oscillococcinum though only one comparison reached statistical significance: Ferley 1989 reported an 18% (95% CI 33%, 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 is that Oscillococcinum reduced temperature by 0.38 Celsius (95% CI 0.15, 0.62).

Adverse events

Most trials did not describe a predefined method for assessment of adverse events. One patient taking Oscillococcinum in 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 Nolleveaux 1990 are excluded from the analysis on grounds of insufficient methodological rigour, the confidence intervals of Attena 1995 alone include differences between groups of clinical value.

There is some evidence that prophylactic use of homeopathy may lead to adverse events (Attena 1995). The reported effects were mild (e.g. 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 is that no assessment of adverse events was planned (Attena: personal correspondence) 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 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 1989 reported a better response to treatment in people aged under 30, this finding was based on an unplanned sub-group 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 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.

REVIEWER'S CONCLUSIONS

Implications for practice

Oscillococcinum probably reduces the duration of illness in patients presenting with influenza symptoms. The evidence is not strong enough to make a general recommendation to use Oscillococcinum for routine treatment. The data do not support the use of homeopathic medicines to prevent influenza and influenza-like syndrome.

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 $5US 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 5% 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 standard deviation (1.73) from the control arms of Ferley 1989 and 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 found 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 1998 (mean 5.29 days; standard deviation 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 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 sub-group analyses to investigate Ferley's finding of a much stronger effect of treatment in patients under 30.

It is open to debate whether further research is warranted on homeopathic medicines to prevent influenza and influenza-like syndrome. Using the control event rate from the meta-analysis of Attena 1995 and 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.

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POTENTIAL CONFLICT OF INTEREST

Nil.

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- No sources of support supplied

REFERENCES

References to studies included in this review

Attena 1995 *{published data only}*
Attena F, Toscano G, Agozzino E, Del Giudice N. A randomized trial in the prevention of influenza-like syndromes by homeopathic management. *Revue d Epidemiologie et de Sante Publique* 1995;**43**:380–2. 95397053.

Casanova 1984 *{unpublished data sought but not used}*
Casanova P. *Tonus* 1984:25–6.

Casanova 1992 *{unpublished data only}*
Casanova P, Gerard R. Oscillococcinum - rassegna della letterature internationale 1992.

Ferley 1989 *{published and unpublished data}*
Ferley JP, Zmirou D, D'Adhemar D, Balducci F. A controlled evaluation of a homoeopathic preparation in the treatment of influenza-like syndromes. *British Journal of Clinical Pharmacology* 1989;**27**:329–35. 89247264.

Nollevaux 1990 *{unpublished data only}*
Nollevaux MA. Unpublished 1992.

Papp 1998 *{published and unpublished data}*
Papp R, Schuback G, Beck E, Burkard G, Bengel J, Lehrl S, Belon P. Oscillococcinum in patients with influenza-like syndromes: a placebo-controlled double-blind evaluation. *British Homoeopathic Journal* 1998;**87**:69–76.

Rottey 1995 *{published data only}*
Rottey EE, Verleye GB, Liagre RL. *Tijdschr Integ Geneeskunde* 1995;**11**:54–8.

References to studies excluded from this review

Bungetzianu 1985
Bungetzianu G. The results obtained by the homeopathical dilution (15 CH) of an antiinfluenzal (Anti-Flu-) vaccine. IN: Proceedings of the 40th Congress of the LMHI (Lyon). 1985:143.

Ferley 1987
Ferley JP, Poutignat N, Azzopardi Y, Charrel M, Zmirou D. *Immunologie Médicale* 1987;**20**:22–8.

Heilmann 1992
Heilmann A. *Biologische Medizin* 1992;**21**:225–9.

Hourst 1982
Hourst P. Unpublished Dissertation, Pitie-Salpetrière: Universite Pierre et Marie Curie 1982.

Lecocq 1985
Lecocq P. *Cahiers de Biothérapie* 1985;**87**:65–73.

Lewith 1989
Lewith G, Brown PK, Tyrell DA. Controlled study of the effects of a homoeopathic dilution of influenza vaccine on antibody titres in man. *Complementary Medical Research* 1989; **3**:22–4.

Masciello 1985
Masciello E, Felisi E. Proceedings of the 40th Congress of the Liga Medicorum Homoeopathica Internationalis (Lyon). 1985:271–4.

Additional references

Kayne 1997
Kayne SB. *Homoeopathic pharmacy*. Edinburgh: Churchill Livingstone, 1997.

Linde 1997
Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, Jonas WB. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997;**350**:834–43. 97456644.

* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**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 200c, once a week for three weeks and then once, one month later
Outcomes	At least one episode of influenza-like syndrome defined as temperature > 37.7 Celsius and two of chills, cough, myalgia, rhinitis or sore throat.
Notes	
Allocation concealment	A

Study	**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. Male: Female 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.

Characteristics of included studies (*Continued*)

Study	**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 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.
Allocation concealment	B
Study	**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 > 12 years; rectal temperature > 38 Celsius and at least two of headache, stiffness, lumbar and articular pain, shivers. Exclusion criteria: duration > 24 hours; immune deficiency; local infection; immunisation against influenza; depression; immunostimulant treatment. Average age verum / placebo: 34 / 35. Male: Female 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 < 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.
Allocation concealment	A
Study	**Nollevaux 1990**
Methods	Treatment allocation: B Performance bias: B Observer blinding: B Exclusions / withdrawals: B
Participants	200 subjects 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 < 25 / 26 -55 / > 55 verum // placebo: 46 / 44 / 9 // 52 / 33 / 7.
Interventions	A variety of inactivated viruses and bacteria prepared homoeopathically to a 200 K potency. 1 pill / fortnight for four months.

Characteristics of included studies (*Continued*)

Notes	Trial described as double-blind but not randomised.
Allocation concealment	B
Study	**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 > 38 Celsius; muscle pain or headache; one of shivering, cough, spinal pain, nasal irritation, malaise, thoracic pain, periarticular pain. Exclusion criteria: duration > 24 hours; immune deficiency; local infection; immunisation against influenza; medical need for medication; immunostimulant or immunosupressive treatment. Use of analgesics, antibiotics or anti-influenzals in the first 48 hours was a post-randomisation exclusion criterion. Average age verum / placebo: 35 / 35. Male: Female verum / placebo:95:93 / 96:88
Interventions	Oscillococcinum three times a day for three days.
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.
Allocation concealment	A
Study	**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. 1 pill / week for 12 weeks.
Outcomes	1Number 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	
Allocation concealment	A

Characteristics of excluded studies

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

Characteristics of excluded studies (*Continued*)

Lecocq 1985	Not Oscillococcinum or an Oscillococcinum-type medicine
Lewith 1989	No clinical outcome measures.
Masciello 1985	Not placebo-controlled.

SUMMARY TABLES

00 Prevention: Oscilloccinum-like medicine v. placebo

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

01 Treatment: Oscillococcinum v. placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
Patient assessment: treatment not a success	3	852	Relative Risk (Random) 95% CI	0.60 [0.37, 0.98]
Patient assessment sensitivity analysis	2	752	Relative Risk (Random) 95% CI	0.75 [0.58, 0.99]
Not recovered at 48 hours	2	834	Relative Risk (Fixed) 95% CI	0.93 [0.88, 0.99]
Not improved at 48 hours	1	372	Relative Risk (Fixed) 95% CI	0.47 [0.29, 0.75]
Number of days to recovery	2	823	Weighted Mean Difference (Fixed) 95% CI	-0.26 [-0.47, -0.05]
Number of days to return to work	2	742	Weighted Mean Difference (Fixed) 95% CI	-0.49 [-0.89, -0.08]
Chills	3	715	Relative Risk (Random) 95% CI	0.63 [0.41, 0.96]
Fever	3	714	Relative Risk (Random) 95% CI	0.34 [0.08, 1.51]
Rhinitis	2	415	Relative Risk (Fixed) 95% CI	0.99 [0.89, 1.09]
Sore throat	1	315	Relative Risk (Fixed) 95% CI	0.99 [0.89, 1.10]
Aches	3	715	Relative Risk (Random) 95% CI	0.60 [0.27, 1.36]
Headache	1	315	Relative Risk (Fixed) 95% CI	0.97 [0.90, 1.05]
Back and side pain	1	315	Relative Risk (Fixed) 95% CI	0.88 [0.78, 0.99]
Spinal pain	1	315	Relative Risk (Fixed) 95% CI	0.91 [0.79, 1.06]
Cough	1	315	Relative Risk (Fixed) 95% CI	1.03 [0.92, 1.14]
Night cough	1	100	Relative Risk (Fixed) 95% CI	0.80 [0.47, 1.36]
Day cough	1	100	Relative Risk (Fixed) 95% CI	0.52 [0.29, 0.93]
Total symptom score	1	315	Weighted Mean Difference (Fixed) 95% CI	-2.01 [-3.41, -0.61]
Temperature	2	614	Weighted Mean Difference (Fixed) 95% CI	-0.39 [-0.52, -0.26]
Use of medication for pain or fever	1	462	Relative Risk (Fixed) 95% CI	0.82 [0.67, 1.00]
Use of medication for cough or sore throat	1	462	Relative Risk (Fixed) 95% CI	0.96 [0.76, 1.21]
Use of antibiotics	1	462	Relative Risk (Fixed) 95% CI	0.87 [0.47, 1.62]
Use of any concomitant medication during trial	1	372	Relative Risk (Fixed) 95% CI	0.83 [0.62, 1.11]

COVER SHEET

Title	Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes
Reviewers	Vickers AJ, Smith C
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