

Amantadine and rimantadine for influenza A in children and the elderly (Review)

Alves Galvão MG, Rocha Crispino Santos MA, Alves da Cunha AJL



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Amantadine and rimantadine for influenza A in children and the elderly (Review)
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[Intervention Review]

Amantadine and rimantadine for influenza A in children and the elderly

Márcia G Alves Galvão², Marilene Augusta Rocha Crispino Santos², Antonio JL Alves da Cunha¹

¹Departamento de Pediatria da Faculdade de Medicina, Instituto de Puericultura e Pediatria Martagao Gesteria - IPPMG, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. ²Municipal Secretariat of Health, Rio de Janeiro, Brazil

Contact address: Antonio JL Alves da Cunha, Departamento de Pediatria da Faculdade de Medicina, Instituto de Puericultura e Pediatria Martagao Gesteria - IPPMG, Federal University of Rio de Janeiro, Av Brig Trompowsky s/n, Cidade Universitaria - Ilha do Fundao, Rio de Janeiro, RJ, 21 940 - 590, Brazil. antonioledo@yahoo.com.br.

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ABSTRACT

Background

Although amantadine (AMT) and rimantadine (RMT) are used to relieve or treat influenza A symptoms in healthy adults, little is known about the effectiveness and safety of these antivirals in preventing and treating influenza A in children and the elderly.

Objectives

The aim of this review was to systematically consider evidence on the effectiveness and safety of AMT and RMT in preventing and treating influenza A in children and the elderly.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2007, issue 3); MEDLINE (1966 to July 2007) and EMBASE (1980 to July 2007).

Selection criteria

Randomised or quasi-randomised trials comparing AMT and/or RMT in children and the elderly with placebo, control, other antivirals or comparing different doses or schedules of AMT and/or RMT or no intervention.

Data collection and analysis

Two review authors independently selected trials for inclusion and assessed methodological quality. Disagreements were resolved by consensus. In all comparisons except for one, the trials in children and in the elderly were analysed separately. Data were analysed and reported using Cochrane Review Manager 4.2. software.

Main results

In children, RMT was effective in the abatement of fever on day three of treatment. AMT showed a prophylactic effect against influenza A infection. AMT and RMT were not related to an increase in the occurrence of adverse effects. RMT also was considered to be well tolerated by the elderly, but showed no prophylactic effect. Different doses were comparable in the prophylaxis of influenza in the elderly, as well as in reporting adverse effects. Zanamivir prevented influenza A more effectively than RMT in the elderly.

Authors' conclusions

AMT was effective in the prophylaxis of influenza A in children. As confounding matters might have affected our findings, caution should be taken when considering which patients should to be given this prophylactic. Our conclusions about effectiveness of both antivirals for the treatment of influenza A in children were limited to a proven benefit of RMT in the abatement of fever on day three of treatment. Due to the small number of available studies we could not reach a definitive conclusion on the safety of AMT or the effectiveness of RMT in preventing influenza in children and the elderly.

PLAIN LANGUAGE SUMMARY

The usefulness of amantadine (Symmetrel®) and rimantadine (Flumadine®) in preventing and treating influenza A in children and the elderly

Influenza A is a respiratory virus in which cough, runny nose, headache and fever are frequent manifestations. Most symptoms usually resolve without treatment within three to seven days. A rare complication of influenza A viruses is that they may develop into a more serious illness leading to hospitalisation, pneumonia and even death, especially among children and the elderly.

This review of trials showed that amantadine can prevent influenza A in children, but it would be necessary to use the drug in up to 14 children during a 14 to 28 weeks period to prevent one case of influenza. New trials are needed to confirm the safety of this drug. We could not reach a conclusion on the use of amantadine in the elderly, as no studies were available.

Although rimantadine was shown to be a safe drug, it cannot be recommended for the prevention of influenza A in children or the elderly as its efficacy has not yet been proven. The only observed benefit of rimantadine in the treatment of children with influenza A was abatement of fever by the third day of treatment, as opposed to four to eight days without this drug. Therefore, rimantadine should be prescribed in selected cases, such as in children with underlying medical conditions in which fever may lead to complications (for example, febrile seizures or dehydration) or in which fever may impair treatment or control of diseases such as diabetes, cardiopulmonary illness, and chronic anemia such as sickle cell disease.

Due to the small number of studies available, we could not reach a definitive conclusion on the safety of amantadine or the effectiveness of rimantadine on preventing influenza in children and the elderly.

BACKGROUND

Description of the condition

Influenza is an acute, usually self-limiting respiratory illness caused by infection with influenza viruses A or B, members of the Orthomyxoviridae family (Nicholson 1992). The illness is characterised by an abrupt onset of symptoms. These symptoms include headache, fever, general aches, weakness and myalgia, accompanied by respiratory tract signs, particularly cough and sore throat. However, a wide spectrum of clinical presentations may occur, ranging from a mild, afebrile upper respiratory illness, to severe prostration and respiratory and systemic signs and symptoms. The most common complication that occurs during outbreaks of in-

fluenza is pneumonia (both viral and bacterial). A number of extra-pulmonary complications may also occur. These include Reye's syndrome in children (most commonly between 2 and 16 years of age), myocarditis, pericarditis and central nervous system (CNS) diseases. Again these include encephalitis, transverse myelitis and Guillain-Barré syndrome (Wiselka 1994).

Description of the intervention

Nowadays there are two main measures for the treatment and prophylaxis of influenza viruses: immunisation using influenza vaccines directly isolated from influenza A and B viruses, and antiviral agents (Demicheli 2000). Although vaccination is the primary

strategy for the prevention of influenza, there are a number of likely scenarios for which vaccination is inadequate and effective antiviral agents would be of utmost importance. During any influenza season, antigenic drift in the virus may occur after formulation of the year's vaccine. So, the vaccine can be less protective, and outbreaks can more easily occur in high-risk populations. In the course of a pandemic, vaccine supplies would be inadequate. Vaccine production by current methods cannot be carried out with the speed required to halt the progress of a new strain of influenza virus; therefore, it is likely that vaccines would not be available for those infected by the first wave of the virus (Hayden 2004). Antiviral agents therefore form an important part of a rational approach to influenza management (Moscona 2005). Antiviral drugs for influenza currently include two classes, each with two drugs: M2 ion channel inhibitors: amantadine (AMT) and rimantadine (RMT), and neuraminidase inhibitors: zanamivir and oseltamivir. M2 ion channel inhibitors affect ion channel activity through the cell membrane. They are reported to be effective by interfering with the replication cycle of type A viruses (but not type B). The neuraminidase inhibitors interfere with the release of progeny influenza virus from infected host cells and are effective against influenza A and B (Moscona 2005). Both drug classes have shown partial effectiveness for prevention and treatment of influenza A viruses, although neuraminidase inhibitors are less likely to promote the development of drug-resistant influenza (Moscona 2005).

How the intervention might work

The efficacy of AMT and RMT for treatment and prevention of influenza A in adults has already been the topic of a review (Jefferson 2006b). Results of that review confirmed that AMT and RMT had a comparable effectiveness in the prevention and treatment of influenza A in healthy adults. Furthermore, previous influenza pandemics proved to be susceptible to this class of drugs. It is reasonable therefore to consider M2 inhibitors in the approach to influenza viruses, if a circulating strain is known to be susceptible to AMT and RMT (Hayden 2006b).

Our aim was to carry out a systematic review focused on the effects and safety of amantadine and rimantadine in children and the elderly, with particular attention to the drug's side effects. Participants aged 20 to 60 were excluded from our review.

Why it is important to do this review

Although the disease occurs in all age groups (Pineda Solas 2006) the risks of complications, hospitalisations, and deaths from influenza are higher among three groups of people. These groups are: 1) persons older than 65 years, 2) young children, 3) and persons of any age who have medical conditions that place them at increased risk. Rates of infection are highest amongst children,

who are also one of the most important links for transmission (Dolin 2005).

In the past 110 years there have been five pandemics caused by different influenza A viral subtypes. The Spanish influenza pandemic (1918 to 1919) is considered to have caused an estimated 40 million deaths world wide. Most years, typical influenza epidemics infects 5 to 20% of the population, and results in anywhere between 250,000 to 500,000 deaths, according to the World Health Organization (WHO), although other estimates accounting for deaths due to complications of influenza are as high as 1 to 1.5 million. Pandemics occur when influenza spreads globally, infecting 20 to 40% of the world population in one year. This results in as many as ten million deaths (WHO 2003). Pandemics usually arise in China where pigs, ducks and humans live in close proximity to each other, and spread westward to the rest of Asia, Europe and the Americas (Bonn 1997).

OBJECTIVES

1. To identify, retrieve and assess all studies evaluating the effects of AMT or RMT on influenza A in children and the elderly.
2. To assess the efficacy of AMT and RMT in preventing cases of influenza A in children and the elderly.
3. To assess the efficacy of AMT and RMT in shortening the duration of influenza A manifestations in children and the elderly.
4. To compare the frequency of adverse effects of AMT and RMT to control groups in children and the elderly.

In comparisons between groups intended for AMT or RMT prophylaxis or treatment compared with control groups the following hypotheses were tested:

- There is no difference in the number of cases of influenza A or in the duration of influenza symptoms;
- There is no difference in the number of adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised studies comparing AMT and/or RMT in children and the elderly with placebo, control drugs, different doses or schedules of AMT and/or RMT or no intervention.

Types of participants

Studies where at least 75% of the population were up to 19 years old or 65 years of age or older were included, as well as trials considering a wider range of age in which data by age subgroups were available were also selected.

Types of interventions

The interventions of interest were the comparisons of AMT and/or RMT to placebo, control drugs, other antivirals, no interventions or different doses of AMT and/or RMT as prophylaxis and/or treatment for influenza A.

Types of outcome measures

Primary outcomes

- **Response to treatment**, measured as cases on the specified day of treatment:

- Fever on day three of treatment; cough on day seven of treatment; malaise on day six of treatment; conjunctivitis and eye symptoms on day five of treatment.

- **Cases of influenza**, studied in all prophylaxis comparisons, including those in which two antivirals (RMT and zanamivir) (Gravenstein 2005; Schilling 1998) and two different doses of RMT were compared (Monto 1995)

- **Cases of side effects in children:**

- Diarrhoea, exanthema, malaise, muscular limb pain, headache, dyspnoea, dizziness, stimulation/ insomnia, nausea, vomiting, arrhythmia, gastrointestinal (GI) symptoms, CNS symptoms, change in behaviour, hyperactivity and tinnitus.

- **Cases of side effects in the elderly:**

- Headache, dizziness, stimulation/ insomnia, nausea, vomiting, anxiety, confusion, fatigue, depression, impaired concentration, loss of appetite, rash or allergic reaction, seizures or clonic twitching, dry mouth, insomnia or sleeplessness, body weakness and debility.

Dichotomous outcomes were used for all the comparisons.

Secondary outcomes

The following outcomes appeared in the protocol but were not considered at the end in the analysis, as they were not reported in the included trials: patients' well-being, admission to hospital, general practitioner's (GP) visits, and other drugs used. Deaths could not be analysed. Although cited by Monto, they were included among other causes of withdrawal (Monto 1995).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2007, issue 3); MEDLINE (1966 to July 2007) and EMBASE (1980 to July 2007).

The MEDLINE and CENTRAL search strategy are shown below. We combined the MEDLINE search string with the Cochrane highly sensitive search strategy phases one and two as published in Appendix 5b of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). See Appendix 1 for the EMBASE search strategy.

MEDLINE (OVID)

```
1 exp INFLUENZA/  
2 influenza.mp.  
3 or/1-2  
4 exp AMANTADINE/  
5 amantadine.mp.  
6 exp RIMANTADINE/  
7 rimantadine.mp.  
8 or/4-7  
9 3 and 8
```

Searching other resources

There were no language or publication restrictions. Bibliography of retrieved articles and reviews were screened in order to identify further trials. Pharmaceutical companies and researches active in the field were contacted for unpublished trials.

Data collection and analysis

Selection of studies

Two review authors (MG, MS) independently read the retrieved trials and applied the selection criteria.

Data extraction and management

MG and MS collected, checked and recorded the following data:

- Setting: hospital, emergency, offices or clinics, primary health care, nursing homes, communities, prisons, force personal, nursery or day care.
- Participants: criteria for patients to join the trial, age, gender, diagnostic criteria and co-morbid conditions.
- Interventions: placebo, other than AMT and RMT antiviral controls, comparing different doses or schedules of AMT and/or RMT or no intervention.
- Outcome measures: global symptom improvements, relief, death, cases of influenza, malaise, fever, nausea, arthralgia, rash, headache, systemic and serious side effects, well-being, admission to hospital, GP's visits, other drugs used, cough, coryza, sore throat, hoarseness, vomiting, abdominal pain, insomnia, irritability, behaviour changes, anorexia.
- Adverse effects: dry mouth, drowsiness/fatigue, constipation, urinary retention, sweating, headache, diarrhoea, palpitations, irritability, blurred vision, dizziness/light headedness, and nausea/vomiting and any other systemic and serious side effects.

Quality assessment

Trials quality was screened by the same two review authors (MG, MS), using the following criteria:

1. Methods of subjects allocation.

- It was assessed if the study was described as randomised.

2. Information on how randomisation sequence was generated and if the process of randomisation was appropriate. Allocation concealment was assessed by the trial author description and classified into four categories:

- Adequate (third party, opaque sealed envelopes).
- Unclear what process used.
- Inadequate (day of the week, alternate).
- Not undertaken.

3. Description of blinding and blinding method.

- The trial was classified as single blind, double blind, triple blind, open label, or not described.
- It was also investigated if participants, clinician and outcome assessor(s) were blinded and the blinding method as: appropriate, effective or unclear.

4. Completeness and length of follow up. Evaluation included:

- Number and the reason of dropouts;
- Completeness and length of follow up.

Arbitration procedure

Disagreements between MG and MS on the quality of the trials were resolved by consensus, although AC had been appointed as arbitrator if necessary.

Data analysis

Two review authors independently applied selection criteria to all retrieved articles and extracted data using a data extraction form, specifically designed for this review. Extracted data were entered the Cochrane Review Manager 4.2 software. Combination of data was dependent on population characteristics and outcomes studied. All the outcomes studied were dichotomous. Risk ratios (RR) and 95% confidence intervals (CI) were calculated for each study. For each outcome, a test of heterogeneity was carried out. Sensitivity analyses were carried out to explore heterogeneity.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Out of a total of 167 abstracts, titles and studies retrieved by the searches, 158 were written in English, three in Russian, two in Czech, two in German, one in French and one in Japanese. Ninety-one studies were discarded. The remaining 76 articles were assessed in detail. It was necessary to contact 45 trial authors to verify if their studies met our selection criteria. Twelve trials were included in this review. All of them are published trials and are described in the 'Characteristics of included studies' table.

The 12 included studies ([Clover 1986b](#); [Clover 1991](#); [Crawford 1988](#); [Finklea 1967](#); [Gravenstein 2005](#); [Hall 1987](#); [Kitamoto 1968](#); [Kitamoto 1971](#); [Monto 1995](#); [Patriarca 1984](#); [Payler 1984](#); [Schilling 1998](#)) were all randomised trials; 11 were blinded and one was unblinded ([Schilling 1998](#)). The methods of randomisation and the follow-up period were poorly described in all studies, although we could estimate that follow-up ranged from 8 to 120 days. We classified the included trials into two major groups:

- Those conducted in children;
- Those in the elderly.

Included studies

Trials in children

Eight selected studies looked at:

1. Treatment with:

AMT (Kitamoto 1968; Kitamoto 1971).

RMT (Hall 1987).

2. Prophylaxis with:

AMT (Finklea 1967; Payler 1984).

RMT (Clover 1986b; Clover 1991; Crawford 1988).

3. Adverse effects due to:

AMT (Kitamoto 1968; Kitamoto 1971)

RMT (Clover 1986b; Crawford 1988; Hall 1987).

For treatment trials and the outcome fever on day three of treatment, the AMT arm size was 51 and the control arm size was 53 children (Kitamoto 1968; Kitamoto 1971). The RMT arm size was 37 and the control arm size was 32 children (Hall 1987). For the other outcomes, cough on day seven, malaise on day six and eye symptoms on day five, just one trial was selected (Hall 1987). The RMT arm size was 37 and control arm size was 32 children for each of these outcomes.

In the five prophylaxis trials we applied wider age ranges for children than the definition stated in the protocol (participants up to 16 years of age). These trials included older participants who were adolescents by WHO definition (WHO 2007). Data regarding the proportion of the subgroup which strictly fulfilled the age criterion were not available in these studies or by contacting the trial authors. The respective age ranges were 1 to 17 years (Clover 1991), 13 to 19 years (Payler 1984), 1 to 18 years (Clover 1986b; Crawford 1988), and 8 to 19 years of age (Finklea 1967).

The AMT arm size was 368 (Finklea 1967: 104, Payler 1984: 264) and the control arm size was 373 children (Finklea 1967: 133, Payler 1984: 240). The RMT arm size was 84 (Clover 1986b: 35, Clover 1991: 22, Crawford 1988: 27) and the control arm size was 94 participants (Clover 1986b: 41, Clover 1991: 24, Crawford 1988: 29).

Reported adverse effect of AMT included exanthema, malaise, muscular limb pain, headache, arrhythmia, stimulation/ insomnia. The antiviral arm size was 264 children (Kitamoto 1968: 75, Kitamoto 1971: 189) and the control arm size was 335 (Kitamoto 1968: 84, Kitamoto 1971: 251).

A reported adverse effect of AMT was dyspnoea. The antiviral arm size was 75 and control arm size was 84 children (Kitamoto 1968). For the adverse effects hyperreactivity and tinnitus the RMT arm size was 27 and the control arm size was 29 children (Crawford 1988).

Nausea/ vomiting, diarrhoea and dizziness were described as possible adverse effects for both antivirals. For nausea/ vomiting, the AMT arm size was 264 children (Kitamoto 1968: 75, Kitamoto 1971: 189) and the control arm size was 335 (Kitamoto 1971: 251, Kitamoto 1968: 84). The RMT arm size was 38 (Crawford 1988: 1, Hall 1987: 37) and control arm size was 61 (Crawford 1988: 29, Hall 1987: 32).

For diarrhoea and dizziness the AMT arm size was 264 children (Kitamoto 1968: 75, Kitamoto 1971: 189) and control arm size was 335 (Kitamoto 1968: 84, Kitamoto 1971: 25). The RMT arm size was 27 and the control arm size was 29 children for these

adverse effects (Crawford 1988).

Trials in the elderly

Three trials were selected in this age group and reported on prophylaxis with RMT. No treatment trials were selected. The following outcomes were studied.

1. Prophylaxis of laboratory and clinical infection (Monto 1995; Patriarca 1984).

2. Adverse reactions (Monto 1995; Patriarca 1984).

3. Different doses of RMT as a prophylactic antiviral (Monto 1995).

4. Comparison to other antivirals in the prophylaxis of influenza (Gravenstein 2005; Schilling 1998).

For prophylaxis of laboratory and clinical infection, the RMT (200 mg/day) arm size was 44 (Monto 1995: 26, Patriarca 1984: 18) and the placebo arm size was 31 participants (Monto 1995: 14, Patriarca 1984: 17). The trial authors stated they limited this analysis to vaccinated participants in nursing homes with confirmed influenza, as it provided an estimate of the additional protective efficacy of RMT. The sample studied by Patriarca 1984 was made up of previously vaccinated participants, so all the participants were analysed (Monto 1995; Patriarca 1984).

In the adverse reaction studies focusing on stimulation/insomnia, confusion, fatigue, nausea, depression, loss of appetite and vomiting, the RMT (200 mg/day) arm size was 150 (Monto 1995: 132, Patriarca 1984: 18) and the placebo arm size was 83 participants (Monto 1995: 66, Patriarca 1984: 17). All randomly assigned participants were analysed.

In the adverse reaction study focusing on headache, impaired concentration, rash or allergic reaction, seizures or clonic twitching, the RMT (200 mg/day) arm size was 132 and the placebo arm size was 66 participants (Monto 1995).

In another adverse reaction study focusing on dizziness and anxiety the RMT (200 mg/day) arm size was 18 and the placebo arm size was 17 participants (Patriarca 1984).

In the unique study evaluating different doses of RMT as a prophylactic drug to clinical and confirmed influenza A, RMT (100 mg/day) arm size was 28 and the RMT (200 mg/day) arm size was 26 participants (Monto 1995).

Only one selected study focused on adverse effects related to different doses of RMT. The studied effects were: confusion, depression, impaired concentration, insomnia or sleeplessness, loss of appetite, rash or allergic reaction, seizure or clonic twitching, dry mouth, fatigue or drowsiness, headache, body weakness and debility. The 100 mg/day arm size was 130 and the 200 mg/day arm size was 132 participants (Monto 1995).

Two trials were selected for the comparison of RMT to another antiviral and the participants were also the elderly (Gravenstein 2005; Schilling 1998). RMT arm size was 254 and zanamivir arm size was 291 participants. No study used AMT for this kind of comparison.

Excluded studies

Ninety-one studies were discarded for the following reasons:

- They were carried out in different age groups;
- They were not controlled trials;
- They assessed other drugs;
- They were non-human or laboratory studies.

Risk of bias in included studies

Allocation

The included trials yielded a mean Jadad's scale (Jadad 1996) score of 3.42, ranging from two to five. The trial authors of the 12 included studies stated that participants had been randomly allocated into treatment or control groups with no mention of any particular randomisation method. In two of the studies (Hall 1987; Payler 1984) we obtained the following information by contacting the trial authors. Hall reported that a computer generated random numbers system had been used. The University Pharmacy was chosen to allocate and store the study drugs (Hall 1987). In Payler's study, randomisation had been carried out by the statistical department of a pharmacy company, which kept the key to the randomisation, and only when the study was analysed was the code broken (Payler 1984).

Blinding

Schilling's study was an unblinded trial (Schilling 1998). Two other studies were not referred to as double-blinded trials (Clover 1991; Payler 1984). As Clover used a placebo, we assumed it was at least a single-blind study (Clover 1991). Information about the duration of the trial was available in all the included studies, but follow up and reasons for withdraw and dropouts were usually unclear.

Effects of interventions

We intended to carry out 12 comparisons, although only eight could be conducted.

Comparisons in children

1. AMT and RMT compared to control (placebo and acetaminophen) in the treatment of influenza A in children.
2. AMT and RMT compared to control (placebo and a specific treatment) in the prophylaxis of influenza A in children.
3. Adverse effects of AMT and RMT compared to control (placebo and acetaminophen) in children.
4. Use of different doses of AMT and RMT for prophylaxis or treatment of influenza A in children.

5. Adverse effects related to different doses of AMT and RMT in children.

6. AMT and RMT compared to other antivirals in children.

Comparisons in the elderly

1. AMT and RMT compared to control in the treatment of influenza A in the elderly.
2. AMT and RMT compared to control (placebo and zanamivir) in the prophylaxis of influenza A in the elderly.
3. Adverse effects of AMT and RMT compared to control (placebo) in the elderly.
4. Use of different doses of AMT and RMT for prophylaxis and treatment of influenza A in the elderly.
5. Adverse effects related to different doses of AMT and RMT in the elderly.
6. AMT and RMT compared to other antivirals in the elderly.

Additional comparison (children plus the elderly)

We made a 13th comparison: the effect of RMT was compared to control (placebo) in the prophylaxis of influenza A in children and the elderly.

Comparisons in children

Comparison 1: AMT and RMT compared to control (placebo and acetaminophen) in the treatment of influenza A in children

Originally in the protocol we planned to study the drug effect on reduction of fever and cough as they are considered the best predictors on influenza diagnosis. After collecting data, we verified that specific timelines for reduction of signs and symptoms were not reported in the included trials. So we searched for another way to present an estimation of the response to AMT and RMT in patients with influenza. For this unplanned analysis, we considered the available data and arbitrarily chose a day of antiviral use to evaluate the response to the treatment. This choice was based on Eccle's study in which clinical manifestations were classified in early and later symptoms (Eccle 2005). Typically fever may last four to eight days, so we chose day three of treatment as the cut off point to which it could be considered that the response to the drug would be useful (Eccle 2005). Cough is considered a later manifestation that develops slowly and can still be present a week later (Eccle 2005). In the same way, we chose day seven of treatment as the cut off point by when the response to the drug could be considered useful.

Finally, we also decided to include other treatment outcomes as they were available in Hall's electronic correspondence to the review authors. In the same way, we arbitrarily chose a day of antiviral use to evaluate the response to the treatment to make this

unplanned analysis: 'malaise on day six', as it begins early but could still be present for one or two weeks (Eccle 2005; Smith 2006) and 'eye manifestations on day five', as it can occur early on in the course of the illness (Treanor 2005; Wright 2004) AMT was compared to placebo (Kitamoto 1968; Kitamoto 1971) and RMT to acetaminophen (Hall 1987).

There was a protective effect of AMT and RMT in the occurrence of fever on day three of antiviral treatment, when trials using both antivirals were combined (Kitamoto 1968; Kitamoto 1971; Hall 1987) RR 0.39; 95% CI 0.20 to 0.79.

The baseline risk of fever on day three of treatment was 0.28, calculated on the basis of the control event rate (CER). The number of children needed to treat to benefit (NNTB) to prevent one case of fever on day three of treatment was 5.88 (95% CI 4.55 to 16.67).

A protective effect of RMT for this outcome was also verified: RR 0.36; 95% CI 0.14 to 0.91. The baseline risk of fever on day three of treatment was 0.38, calculated on the basis of the CER. The NNTB to prevent one case of fever on day three of treatment was 4.12 (95% CI 3.03 to 33.33). Just one study reported this outcome (Hall 1987).

No protective effect of AMT was observed in the occurrence of fever on day three of treatment: RR 0.37; 95% CI 0.08 to 1.75 (Kitamoto 1968; Kitamoto 1971).

No protective effect of RMT was seen regarding the occurrence of any of the following outcomes assessed: cases of pain on movement and visual distortion on day five (RR 0.58; 95% CI 0.10 to 3.24), conjunctivitis on day five (RR 0.17; 95% CI: 0.01 to 3.49), malaise on day six (RR 1.04; 95% CI 0.63 to 1.70), and cough on day seven (RR 0.83; 95% CI 0.63 to 1.10). Just one study reported this outcome (Hall 1987).

No selected studies reported the use of AMT for these latter outcomes.

Comparison 2: AMT and RMT compared to control (placebo and to specific treatment) in the prophylaxis of influenza A in children

AMT was compared to placebo and specific treatment (Finklea 1967; Payler 1984) and RMT to placebo (Clover 1986b; Crawford 1988; Clover 1991)

The AMT (Finklea 1967; Payler 1984) and RMT trials (Clover 1986b; Clover 1991; Crawford 1988) were heterogeneous (Chi^2 9.27, $P = 0.05$, $I^2 = 56.8\%$) and could not be combined. A protective effect of AMT was observed with a RR 0.11; 95% CI 0.04 to 0.30. The baseline risk of influenza was 0.10, calculated on the basis of the CER. The NNTB was 11.1 (95% CI 10 to 14.29) for a period ranging from 14 (Payler 1984) to 18 weeks (Finklea 1967).

On the other hand, no protective effect of RMT was seen in the prophylaxis of cases of influenza (RR 0.49; 95% CI 0.21 to 1.15) (Clover 1986b; Clover 1991; Crawford 1988).

Comparison 3: adverse effects of AMT and RMT compared to control (placebo and acetaminophen) in children

AMT was compared to placebo (Kitamoto 1968; Kitamoto 1971). RMT was compared to placebo (Clover 1986b; Crawford 1988) and to acetaminophen (Hall 1987).

AMT was not related to a higher risk of the following adverse effects: diarrhoea (RR 0.79; 95% CI: 0.42 to 1.47), exanthema (RR 0.69; 95% CI 0.21 to 2.34), muscular limb pain (RR 0.85, 95% CI 0.46 to 1.59), headache (RR 0.73; 95% CI 0.52 to 1.03), and stimulation and insomnia (RR 0.46; 95% CI: 0.12 to 1.74) (Kitamoto 1968; Kitamoto 1971).

In the same way, AMT was not related to the outcomes dizziness and dyspnoea. For dizziness the RR was 6.63 (95% CI: 0.32 to 137.33) (Kitamoto 1968; Kitamoto 1971) and for dyspnoea the RR was 0.37 (95% CI 0.02 to 9.02) (Kitamoto 1968).

The studies were heterogeneous for the outcomes malaise ($\text{Chi}^2 = 3.75$, $P = 0.05$, $I^2 = 73.3\%$) and nausea/ vomiting ($\text{Chi}^2 = 4.26$, $P = 0.04$, $I^2 = 76.5\%$), although it seems that the author had used the same protocol. Nevertheless the heterogeneity for the outcome nausea/ vomiting does not seem to be relevant as AMT could be related either to an increase or to a reduction in the occurrence of this adverse effect (Kitamoto 1968; Kitamoto 1971).

No cases of arrhythmia were reported in those two trials.

RMT was not related to a higher risk of any of the following adverse effects assessed: CNS symptoms (RR 0.23; 95% CI 0.01 to 4.70); change in behaviour (RR 0.23; 95% CI 0.01 to 4.70); diarrhoea (RR 0.36; 95% CI 0.02 to 8.41); dizziness (RR 3.21; 95% CI 0.14 to 75.68); GI manifestations (RR 1.17; 95% CI 0.08 to 18.05); hyperactivity (RR 0.36; 95% CI 0.02 to 8.41); tinnitus (RR 3.21; 95% CI 0.14 to 75.68); and cerebellar ataxia (RR 2.61; 95% CI 0.11 to 61.80) (Clover 1986b; Crawford 1988; Hall 1987).

Each one of the adverse effects described above was studied in just one included study, except for nausea and vomiting (Crawford 1988; Hall 1987). In the same way, RMT was not related to a higher risk of nausea and vomiting: RR 0.96; 95% CI 0.10 to 9.01.

Comparison 4: use of different doses of AMT and RMT for prophylaxis and treatment of influenza in children

There was no selected study conducted in children for this comparison.

Comparison 5: adverse effects related to different doses of AMT and RMT in children

There were no selected studies conducted in children for this comparison.

Comparison 6: AMT and RMT compared to other antivirals in children

There was no selected study conducted in children for this comparison.

Comparisons in the elderly

Comparison 7: AMT and RMT compared to control in the treatment influenza A in the elderly

There was no study selected for this comparison.

Comparison 8: AMT and RMT compared to control (placebo and zanamivir) in the prophylaxis of influenza A in the elderly

RMT to placebo (Monto 1995; Patriarca 1984) and to zanamivir (Schilling 1998). No protective effect of RMT was seen regarding the prophylaxis of influenza in the elderly: RR 0.74; 95% CI 0.13 to 4.07.

Although care must be taken in the interpretation of the Chi^2 test since its low power in detecting heterogeneity in meta-analyses, we should emphasise the high P value observed in this comparison, nevertheless the I^2 value under 50%: $\text{Chi}^2 = 3.28$; $P = 0.19$, $I^2 = 39\%$). We decided to explore the reasons of these findings as if the studies were heterogeneous, even though it would result in smaller samples impairing reaching to any definitive conclusion (Monto 1995; Patriarca 1984; Schilling 1998).

Monto and Patriarca analysed previously vaccinated participants in blinded trials and used a placebo as control (Monto 1995; Patriarca 1984). Schilling did not state if the participants were vaccinated, although it was stated that the majority of the studied population had been previously immunised (Schilling 1998). This was an unblinded trial in which another antiviral (zanamivir) was used as a control drug.

When we excluded this study (Schilling 1998), the remaining trials (Monto 1995; Patriarca 1984) were shown to be homogeneous, but no protective effect of RMT prophylaxis in the occurrence of cases of influenza persisted (RR 0.45; 95% CI 0.14 to 1.41).

Monto 1995 used two different doses of RMT in his trial (100 and 200 mg/day) and Patriarca 1984 used the conventional dose of 200 mg/day. Schilling 1998 used a single dose of 100 mg/day. We also combined Monto's 200 mg/day subgroup with Patriarca's study in which the same dose was administered, but again no protective effect of RMT was observed in the prophylaxis of influenza: RR 0.44; 95% CI 0.12 to 1.63 (Monto 1995; Patriarca 1984; Schilling 1998).

Schilling's sample and Monto's 100 mg/day subgroup were heterogeneous and could not be combined ($\text{Chi}^2 = 2.55$, $P = 0.11$, $I^2 = 60.8\%$) (Monto 1995; Schilling 1998).

There was no AMT study selected for comparison.

Comparison 9: adverse effects of AMT and RMT compared to control (placebo) in the elderly

There were two selected studies for these outcomes, both using RMT and placebo (Monto 1995; Patriarca 1984).

No effect of RMT was seen regarding any of the adverse outcomes assessed in the combined studies: stimulation and insomnia (RR 1.61; 95% CI 0.43 to 6.02), confusion (RR 0.79; 95% CI 0.40 to 1.56), fatigue (RR 0.81; 95% CI 0.41 to 1.60) and vomiting (RR 0.99, 95% CI 0.38 to 2.60) (Monto 1995; Patriarca 1984).

In the same way, RMT was not related to the outcomes studied by Monto: headache (RR 0.83; 95% CI 0.21 to 3.38); impaired concentration (RR 0.50; 95% CI 0.10 to 2.41); rash or allergic reaction (RR 3.53; 95% CI 0.18 to 67.28); seizures or clonic twitching (RR 2.00; 95% CI 0.23 to 17.54) and dry mouth (RR 0.70; 95% CI 0.23 to 2.12), as well as in those studied by Patriarca: dizziness (RR 0.94; 95% CI 0.15 to 5.97) and anxiety (RR 2.83; 95% CI 0.92 to 8.74) (Monto 1995; Patriarca 1984).

The articles were heterogeneous just for the occurrence of nausea (test for heterogeneity: $\text{Chi}^2 = 2.02$; $P = 0.16$; $I^2 = 50.5\%$). Nevertheless, this heterogeneity does not seem to be relevant as RMT could be related either to an increase or to a reduction in the occurrence of nausea in each one of the studies: Patriarca: RR 5.67; 95% CI 0.76 to 42.32, Monto: RR 1.17; 95% CI 0.47 to 2.90 (Monto 1995; Patriarca 1984).

It is important to stress the small samples studied in both trials. There was no AMT trial selected for comparison.

Comparison 10: use of different doses of AMT and RMT for prophylaxis and treatment of influenza A in the elderly

A reduced RMT dose of 100 mg/day was comparable to the full dose of 200 mg daily for prophylaxis of influenza in the elderly, although a wide CI was verified (RR 0.93; 95% CI 0.21 to 4.20). It should be emphasised that there were few data available for these comparisons (Monto 1995).

There was no selected study using different doses of RMT in the elderly, nor any selected trial comparing different doses of AMT for prophylaxis and treatment of influenza in the elderly.

Comparison 11: adverse effects related to different doses of AMT and RMT in the elderly

There was no protective effect of a reduced dose of RMT in the occurrence of the following adverse reactions in the elderly: confusion (RR 0.83; 95% CI 0.41 to 1.65), depression (RR 0.44; 95% CI 0.12 to 1.65), impaired concentration (RR 0.68; 95% CI 0.11 to 3.98), insomnia or sleeplessness (RR 1.02; 95% CI 0.26 to 3.97), loss of appetite (RR 0.62; 95% CI 0.27 to 1.46), rash or allergic reaction (RR 0.34; 95% CI 0.04 to 3.21), seizures or clonic twitching (RR 0.11; 95% CI 0.01 to 2.07), dry mouth (RR 1.16; 95% CI 0.43 to 3.11), fatigue or drowsiness (RR 1.14;

95% CI 0.45 to 2.87), headache (RR 1.02; 95% CI 0.30 to 3.42), and body weakness or debility (RR 0.91; 95% CI: 0.38 to 2.18) (Monto 1995).

There was no AMT trial selected for this comparison in the elderly.

Comparison 12: AMT and RMT compared to other antivirals in the elderly

In Gravenstein's, but not in Schilling's study identical placebo was used (Gravenstein 2005; Schilling 1998). When RMT was compared to zanamivir it was shown that zanamivir prevented influenza A more effectively than RMT in the elderly (Gravenstein 2005; Schilling 1998).

There was no AMT trial selected for this comparison in the elderly.

Additional comparison (children plus the elderly)

Comparison 13: RMT compared to control (placebo) in the prophylaxis of influenza A in children and the elderly

Originally in the protocol we planned only to make the above 12 comparisons. However, whilst analysing data we considered doing an additional comparison and put the two age groups together. As the small samples studied in RMT trials for prophylaxis might have influenced the observed results, we tried to overcome this limitation by combining the trials with RMT in children and in the elderly. RMT had no proven effect in preventing influenza in either age group, but could be effective when we combined the results from both groups. However, it must be stressed that extraneous characteristics between those groups, other than age or previous immunisations, may have occurred, impairing generalisation of these results. There were five studies selected for this comparison (Clover 1986b; Clover 1991; Crawford 1988; Monto 1995; Patriarca 1984) with 156 patients in the treatment group and 125 in the placebo control group. The combination of the trials showed a protective effect of RMT in preventing influenza A (RR 0.49; 95% CI 0.27 to 0.92).

The baseline risk of influenza A was 0.22, calculated on the basis of the CER. The NNTB was 9.09 (95% CI 6.25 to 50). We should emphasise that the follow up period ranged from 3 to 11 weeks.

DISCUSSION

A comprehensive search strategy was used and every effort was made to identify relevant studies. In the majority of our comparisons, drawing definitive conclusions was impaired by the small number of selected articles and the small sample numbers. The studies demonstrated a decreased incidence of influenza A in children using AMT during a period ranging from 14 to 18 weeks.

The NNTB indicates that for every 10 to 14 children receiving AMT, one case of influenza A can be prevented.

RMT had no proven effect in preventing influenza in either age group, but could be effective when we combined the results of both groups. The possibility must be stressed that extraneous characteristics between those groups, other than age or previous immunisations, may have occurred, impairing generalisation of these results. Multiple comparisons should also be taken into account in the interpretation of these results.

When AMT and RMT were combined, they showed to prevent the occurrence of fever on day three in children. However, when analysed separately, this effect was confirmed only for RMT. It must be emphasised that there was just one RMT selected trial for this outcome (Hall 1987) in which the baseline risk for the occurrence of fever on day three was 38%. For every 4.12 children (ranging from 3.03 to 33.33) treated with RMT in this unique small sample, it would be possible to prevent one case of fever on day three of treatment.

It could be suggested that AMT is well tolerated by children, as its use was not related to an increase in the occurrence of the analysed adverse effects. Nevertheless, it may be difficult to distinguish between an adverse effect to the drug and a clinical manifestation of influenza itself. The outcomes muscular pain, headache, malaise, diarrhoea and nausea/ vomiting may be adverse effects of AMT as well as clinical manifestations of influenza in children (MS 2006). In the same way, the outcome dyspnoea (Kitamoto 1968) may also occur due to other respiratory diseases, such as asthma, since an asthmatic episode may be triggered by respiratory viruses. So we must emphasise that adverse effects of the drug and clinical manifestations of influenza may have been confounded, since the selected trials were carried out in ill children.

RMT, administered exclusively on a prophylactic basis, was not related to an increase in the occurrence of the analysed adverse effects. In contrast to AMT studies, just nausea/vomiting could be confounded with influenza manifestations. The other adverse effects could not be confounded, as two of the three selected studies were about prophylaxis and were conducted in children without influenza (Clover 1986b; Crawford 1988). The third study (Hall 1987) was the only one carried out in children with influenza. Cerebellar ataxia and nausea/vomiting were the studied adverse effects in this trial. Cerebellar ataxia could not be confounded as it had not been described as an influenza manifestation. Cases of nausea/vomiting, which were also cited by Crawford, could have been confounded with influenza manifestations in Hall's article. The side effects nausea/vomiting were described in two studies (Crawford 1988; Hall 1987) while all the other adverse effects were mentioned in just one: diarrhoea, dizziness, hyperreactivity, tinnitus (Crawford 1988), GI symptoms, CNS symptoms, changes in behaviour (Clover 1986b), and cerebellar ataxia (Hall 1987). RMT also was considered to be well tolerated by the elderly, since

it was not related to an increase in the incidence of adverse effects in this age group. But the studied samples were even smaller in the elderly than in children's age group and this fact may have influenced our results (Monto 1995; Patriarca 1984).

When analysing the antivirals adverse reactions, we could not even try to overcome the limitation of the small number of articles and the small samples studied by combining the results of both age groups, as the trial authors had described different outcomes (Clover 1986b; Crawford 1988; Hall 1987; Kitamoto 1968; Kitamoto 1971; Monto 1995; Patriarca 1984).

Comparison of different doses of antiviral drugs was available only for RMT and was tested in only one study related to the elderly group. There was no selected trial regarding the treatment either in children or in participants using AMT in both age groups. Both doses showed to be comparable in the prophylaxis of influenza as well as in the occurrence of adverse effects with no proven efficacy (Monto 1995).

Data on comparison to other antivirals was available just for RMT and zanamivir for prophylaxis of influenza A in the elderly group. This fact allowed a comparison of drugs of the two different classes of antivirals: M2 ion channel inhibitors and neuraminidase inhibitors. Zanamivir more effectively prevented influenza A in the elderly group (Gravenstein 2005; Schilling 1998). Although the M2 ion channel inhibitors are increasingly subject to viral resistance (Goodman 2006) it does not mean that we should abandon AMT and RMT. These antivirals proved effective for prophylaxis against influenza illness in the 1968 pandemic of 'Hong Kong influenza' and in 1977 pandemic-like event involving 'Russian influenza'. Although the same resistance marker (Ser31Asn) was present in two isolates of influenza A (H5N1) obtained from patients in China in 2003 and in one lineage of avian and human H5N1 viruses in Thailand, Vietnam, and Cambodia, most tested isolates from a second lineage that had been circulating in Indonesia, China, Mongolia, Russia, and Turkey appear to be sensitive to AMT (Hayden 2005). Furthermore, the next pandemic virus may be one that, like H2N2, is susceptible to this class of drug. If the circulating strain were known to be susceptible to M2 inhibitors, these drugs would offer a less costly alternative to other antivirals (neuraminidase inhibitors) for prophylaxis against illness.

AUTHORS' CONCLUSIONS

Implications for practice

According to available data, AMT was effective in prophylaxis against influenza A in children. The safety of the drug was not well established but it should be tried if one takes into account the important role of children in transmitting infections.

Currently, RMT cannot be recommended as a prophylactic drug for either age group. Nevertheless, if we consider: 1) it is a safe drug;

2) the results of the combined age groups, and 3) the possibility that the next pandemic virus is susceptible to this class of drug, as described in former pandemics, we can still consider this 'old' drug as a less costly alternative to neuraminidase inhibitors.

Our conclusions regarding the effectiveness of both antivirals for the treatment of influenza A in children was limited to a proven benefit of RMT in the abatement of fever by day three of treatment with RMT. This benefit does not seem to justify a recommendation for using RMT to treat all children with influenza A infection, but only for selected cases in which fever may cause undesirable consequences.

We could not reach a conclusion regarding AMT in the elderly, or about antiviral treatment in this age group, as no trials fulfilled our selection criteria.

Caution must be taken when considering the results, as multiple comparisons were developed using the same sample. Therefore, it is possible that statistically significant results could have occurred by chance.

Implications for research

Definitive conclusions may have been impaired by the small number of selected studies and the small sample numbers used.

Further research is necessary for:

Treatment

AMT for the treatment of influenza A in children to increase the sample numbers and the power of the studies.

RMT for the treatment of influenza A in children in order to confirm the observed result from the only selected study and to see if the drug could be useful in treating other clinical manifestations of influenza.

AMT and RMT for the treatment of influenza A in the elderly, as no identified studies fulfilled our inclusion criteria.

Prophylaxis

RMT in children to increase the sample numbers and the power of the studies, in order to achieve more definitive conclusions.

AMT in the elderly as there was no identified studies fulfilling our inclusion criteria for this age group.

RMT in the elderly to increase the sample numbers and the power of the studies, in order to achieve more definitive conclusions.

Adverse effects

AMT in children without influenza to avoid confounding adverse reactions of the antiviral with clinical manifestations of influenza.

RMT in the elderly to increase the sample numbers and the power of the studies.

Different doses of AMT and RMT

Further information is necessary on both drugs in both age groups.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Clover 1986b

Methods	Randomised, parallel, double blind comparison of RMT with PB. The trial took place during an outbreak of influenza A/H1N1 in Oklahoma. Study duration: five weeks. Patients and providers were blinded. Outcome assessor method of blinding was unclear. Dropouts: three families who moved outside the study area, one in the placebo group whose parents attributed the 'medication' to the reducing the child's performance at school, and one in the RMT group due to a non-influenza illness in a four year old child. Co-interventions and other potential confounders were not observed
Participants	There was a total of 146 participants, including 76 children which was our subgroup of interest. Inclusion criteria: children within 35 families during a naturally occurring outbreak of influenza A. Exclusion criteria: if any family member was known to have cardiac, pulmonary, or neurologic disease; if a female family member was pregnant or actively trying to become pregnant; if any family member had received the influenza vaccine during the past year; if any member was taking medications that might interfere with the study. Gender: both females and males were included (proportion not specified) Disease stage: RMT was administered as a prophylactic when influenza A was identified within community
Interventions	RMT: 5 mg/kg/d, max: 100 mg/ d (< 10 years) or 200 mg/ d (> 10 years). Oral route. Duration: five weeks
Outcomes	Laboratory proved infection cases and reported adverse effects
Notes	1 to 18 years old

Risk of bias

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

Clover 1991

Methods	Randomised, parallel, comparison of RMT with PB. Multicentre trial that took place during an influenza season for three to four weeks after the start of treatment. Patients were blinded. Outcome assessor blinding was unclear. Dropouts: none (in the subgroup of interest), co-interventions and other potential confounders were not observed
Participants	There was a total of 84 participants, including 46 children which was our subgroup of interest. Inclusion criteria: children within families consisting of two to five members with at least one adult (ranging in age from 18 to 75 years and one child aged between 1 to 17 years during a naturally occurring outbreak of influenza A. Exclusion criteria: subjects who had a history of AMT hypersensitivity, chronic respiratory disease, severe medical illness, neuropsychiatric disorder; were pregnant or lactating; had a recently documented influenza A virus infection; required long-term drug therapy with AMT or drugs that could interfere with RMT or with clinical assessments (e.g., aspirin, tranquilizers, antihistamines and decongestants. Gender: unclear. Disease stage: all the eligible subjects were given the assigned drug as soon

Clover 1991 (Continued)

	as influenza was first recognised in family members (the index patient) and after the member had been evaluated by a study nurse	
Interventions	RMT: 5 mg/kg/d, max: 150 mg/ d (= or < 10 years or weighing less than 30 kg) or 200 mg/d (> 9 years who weighed more than 30 kg). Oral route. Duration: 10 days	
Outcomes	The outcome of interest was laboratory proved infection cases	
Notes	1 to 17 years old	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Crawford 1988

Methods	Randomised, parallel, double blind trial in which prophylactic efficacy of RMT against influenza A infection in children was evaluated. RMT was compared to PB. The trial took place during a naturally occurring outbreak of influenza A (H3N2) in Oklahoma City, USA, from November, 1984 to March, 1985. Study duration: five weeks. Withdrawal: three children in the RMT group were found post-study to have had documented influenza A infection before or on the day of institution of prophylaxis and were excluded from the analysis. Seventeen people from five families withdrew because of relocation or refusal to have a second blood specimen drawn. Their age group was not stated	
Participants	There was a total of 110 participants from 29 families, including 56 children which was our subgroup of interest. Inclusion criteria: children within 29 families during a naturally occurring outbreak of influenza A infection. Exclusion criteria: if any family member was known to have cardiac, pulmonary, or neurologic disease; if a female family member was pregnant or actively trying to become pregnant; if any family member had received the influenza vaccine during the past year; if any member was taking medications that might interfere with the study. Gender: both females and males were included (proportion not specified). Disease stage: RMT was administered as a prophylactic when influenza A was identified within community	
Interventions	RMT: 5 mg/kg/d, max: 100 mg/d (< 10 years) or 200 mg/d (> 10 years). Oral route	
Outcomes	Laboratory proved infection cases. Adverse effects	
Notes	1 to 18 years old	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Finklea 1967

Methods	Randomised, parallel, double blind, trial in which AMT use as prophylaxis in naturally-occurring acute respiratory illness. AMT was compared to PB. The trial took place between February 1965 to June 1965. The method of blinding is unclear. Study duration: 18 weeks. Withdrawal was the same for the two groups - discharge from school (19%). The proportion was not stated	
Participants	There were 293 participants from both sexes (proportion not stated), from 8 to 19 years of age. The subjects were volunteers at a school for intellectually handicapped but educateable children. Sera pairs tests were obtained in 237 children. Exclusion criteria: children receiving tranquilizers, sympathomimetic amines or anticonvulsives. Co-morbid conditions: intellectually handicapped children	
Interventions	AMT: 1 to 2.5 mg/kg. (Pre-puberal: 60 mg/ dose, 2 x/d, during the first week and 1 X/d during the rest of the period of the study. Older children: 100 mg/dose, 2 x/d, during the first week and 1 x/d during the rest of the period of the study	
Outcomes	Fourfold rises in CF and/or HI titer against A2/AA/1/65	
Notes	8 to 19 years old	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Gravenstein 2005

Methods	Randomised, parallel, double blind comparison of RMT with zanamivir. Identical PB (inhaled or tablets) were used. The trial took place in nine long-term care facilities in the United States over three winter seasons. Because the study was conducted over multiple influenza seasons, some subjects were randomised more than once. Study duration: three winter seasons. Co-interventions and other potential confounders were not observed	
Participants	There were 231 subjects in the RMT group and 226 in the zanamivir group (intent-to-treat population) of both sexes (29% female in RMT group and 30% female in zanamivir group. More than 75% of the subjects were 65 years of age or older (90% in RMT group and 89% in zanamivir group)	
Interventions	Upon an influenza outbreak subjects were randomised (1:1) to inhaled zanamivir plus PB or inhaled PB plus zanamivir 100 mg tablets for 14 days	
Outcomes	The outcome of interest was laboratory proved infection cases	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hall 1987

Methods	Randomised, parallel, double blind comparison of RMT with acetaminophen. Study duration: seven days. One patient dropped out, due to AE. Co-interventions and other potential confounders were not observed
Participants	69 children were included, 40 females and 29 males. The inclusion criteria were: clinical illness and viral isolation. Exclusion criteria: previously unhealthy aged 1 to 15 years. Disease stage: clinical illness and confirmed laboratory infection
Interventions	RMT: 6.6 mg/ kg/d, max: 150 mg/d (< 9 years) and 200 mg/d (>= 9 years), 2 x/d; by oral route, for 5 days
Outcomes	Mean symptom score of: fever, conjunctivitis, eye symptoms (pain on movement, fever up to 3rd day, conjunctivitis up to 3rd day, eyes symptoms (pain on movement and visual distortion); cough up to 7th day; malaise up to 6th day; CNS symptoms
Notes	

Risk of bias

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

Kitamoto 1968

Methods	Randomised, parallel, double blind comparison of AMT with PB. This trial took place during an outbreak of influenza in Japan. Study duration: seven days. Patient, provider and outcome assessor method of blinding is unclear. Dropouts: none Co-interventions and other potential confounders were not observed.
Participants	There were 355 participants. Although the proportions are not cited, it's stated that the groups are comparable in the following criteria: sex, age, influenza vaccination history, distribution and geometric mean of HI and CF titer in acute sera, interval between onset of symptoms and start of treatment, and maximum body temperature before the treatment. 158 subjects of both genders met the age criteria. 91 children were cases of clinical influenza with serological confirmation The proportion of males and females was not stated. Inclusion criteria: respiratory symptoms evident within the 2nd day of illness. Disease stage: clinical symptoms within 2nd day of illness
Interventions	AMT: 50 mg/d (one to two years old); 100 mg/d (three to five years old); 150 mg/d (6 to 10 years old), by oral route, for seven days
Outcomes	Fever up to 4th day. AE: nausea/ vomiting; diarrhoea; exanthema; malaise; muscular, limb pain; headache; dyspnoea; cyanosis; stimulation/ insomnia; dizziness; arrhythmia
Notes	

Risk of bias

Item	Authors' judgement	Description
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Kitamoto 1968 (Continued)

Allocation concealment?	Unclear	B - Unclear
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Kitamoto 1971

Methods	Randomised, parallel, double blind comparison of AMT with PB. The trial took place during an outbreak of influenza in the winter of 1968 to 1969 in Japan. The study duration was at least seven days. Patient, provider and outcome assessor method of blinding was unclear. Dropouts were not stated. Co-interventions and other potential confounders: concomitant administration of antipyretics. It was also performed an analyses with patients who received concomitant antipyretics	
Participants	Of the 737 participants, 155 subjects of both genders met the inclusion criteria. Although the proportions are not cited, it is stated that the groups are comparable in the following criteria: sex, age, influenza vaccination history, distribution and geometric mean of HI and CF titer in acute sera, interval between onset of symptoms and start of treatment, and maximum body temperature before the treatment. Inclusion criteria: respiratory symptoms evident within the 2nd day of illness. Disease stage: clinical symptoms within 2nd day of illness	
Interventions	AMT: 50 mg/d (one to two years old); 100 mg/d (three to five years old); 150 mg/d (6 to 10 years old), by oral route, for seven days	
Outcomes	Fever up to 4th day. AE: nausea/ vomiting; diarrhoea; exanthema; malaise; muscular, limb pain; headache; stimulation/ insomnia; dizziness; arrhythmia	
Notes		

Risk of bias

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

Monto 1995

Methods	Randomised, parallel, double blind comparison of two different doses of RMT with PB. The trial took place during an outbreak of influenza A/H3N2 during 1993. Study duration: eight weeks. 62% withdrew because of side effects, death, discharge, hospitalisation, physician's request and refusal to continue participation. Co interventions and other potential confounders were not observed	
Participants	A total of 328 participants, 275 females and 53 males were included. Inclusion criteria: residents of 10 nurse homes who agreed to participate in the study. Exclusion criteria: patients with significant renal or hepatic disease. Disease stage: RMT was administered as prophylaxis	
Interventions	RMT: 100 mg/d; RMT: 200 mg/d; PB. Ratio: 2:2:1 Duration: up to eight weeks	
Outcomes	Death. Adverse effects: dry mouth, drowsiness/ fatigue, headache, irritability, dizziness/ light headedness, nausea/ vomiting, abdominal pain, body weakness or disability, confusion, depression, impaired concentration, insomnia or sleeplessness, loss of appetite, rash or allergic reaction, seizure or clonic twitching	

Monto 1995 (Continued)

Notes	Three groups: RMT 100 AMT 200 and PB	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Patriarca 1984

Methods	Randomised, parallel, double blind comparison of RMT with PB. The trial took place during an outbreak of influenza A (H3N2) viruses were isolated from patients in the community. The study was conducted from early January 1983 to 6 April. Patient, provider and outcome assessor method of blinding is unclear	
Participants	35 participants, 68 to 102 years old, of non-specified gender, all of whom had been vaccinated the previous autumn. Inclusion criteria: residents of three nursing homes who agreed to participate in the study. Exclusion criteria: patients with medical conditions that might increase the severity of side effects or require careful adjustments in the dosage of RMT, which include: significant renal impairment (SCr > 2 mg/d) or liver disease, acute congestive heart failure, seizure disorders, psychosis, severe pitting oedema, orthostatic hypotension, and conditions requiring central nervous system stimulants Disease stage: RMT was administered as prophylaxis	
Interventions	RMT: 100 mg twice a day; PB. Duration: 80 (+/- 4,9) days prophylaxis	
Outcomes	Adverse reactions: anxiety, confusion, insomnia, anorexia, fatigue, dizziness, nausea and vomiting	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Payler 1984

Methods	Randomised, parallel trial. Blindness is not stated. AMT use as prophylaxis in naturally-occurring acute respiratory illness. AMT was compared to no specific treatment. The trial took place in the autumn of 1982. Study duration: 14 days. Patients excluded from analysis were similar in the two groups and the reasons were: students were day boys from whom samples were not available: students infected before the start of AMT; compliance failures	
Participants	There were 604 randomised students and 536 were analysed. All of them were male, from 13 to 19 years of age. The subjects were students of a boarding school. Once influenza A outbreak had been detected, samples were taken from all boys who were sufficiently unwell to be absent from lessons even if they did not have a fever. Nasopharyngeal aspirates were examined for viruses by rapid immunofluorescent microscopy and tissue culture. Once outbreaks had been identified, only culture methods were used	

Payler 1984 (Continued)

Interventions	AMT: 100 mg/ dose, 1 x/d, during the 14 days	
Outcomes	Clinical and laboratory- proved influenza A	
Notes	13 to 19 years old	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Schilling 1998

Methods	Randomised, parallel, unblinded trial. RMT and zanamivir were compared for prophylaxis of influenza A. The trial began in November 1996. Drug administration: 14 days. Number of respiratory illness was monitored until January 1997. The subjects were volunteers residents of a nursing home for veterans and their spouses. Inclusion criteria: volunteers living in a unit of the nursing home where outbreak of influenza was declared. Exclusion criteria: symptoms of new respiratory illness within the previous seven days of the declared outbreak	
Participants	65 volunteers of both sexes received zanamivir and 23 rimantadine were analysed. Age range: 50 to 95 years old and 75% older than 65 years of age. The subjects were volunteers residents of a nursing home for veterans and their spouses. Inclusion criteria: volunteers living in a unit of the nursing home where outbreak of influenza was declared	
Interventions	RMT: 100 mg/dose, 1 x/day, during 14 days. Zanamivir: 10 mg inhaled bid and 4.4 mg intranasally bid	
Outcomes	Clinical and laboratorial proved influenza A	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

ACM: acetaminophen

AE: adverse effects

AMT: amantadine

d: day

NC: not clear

PB: placebo

RMT: rimantadine

SCR: serum creatinine

CNS: central nervous system
 GI: gastrointestinal
 STGO: aspartate aminotransferase
 CF: complement fixation
 HI: Hemagglutination inhibition
 bid: twice a day

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

AAPCID 2007	Not an RCT
Allen 2006	Not an RCT
Anonymous 2006	Not an RCT
Anonymous 2007	Article about oseltamivir and vaccination
Aoky 1985a	Pharmacokinetics study of AMT and RMT
Aoky 1985b	Ages of participants were outside protocol age range
Aoky 1986	Ages of participants were outside protocol age range
Atmar 1990	Ages of participants were outside protocol age range
Baker 1969	Ages of participants were outside protocol age range (participants were aged between 17 to 57 years old)
Barr 2007	Not an RCT
Barr 2007b	Not an RCT
Bauer 2007	Non-human trial
Belenky 1998	Ages of participants were outside protocol age range (participants were aged between 17 to 57 years old)
Bloomfield 1970	Ages of participants were outside protocol age range
Brady 1990	Ages of participants were outside protocol age range
Bricaire 1990	Analyses by age subgroups of interest were not available
Bryson 1990	Insufficient data available
Callmander 1968	Ages of participants were outside protocol age range (participants were 20 to 60 years old)
Chemaly 2006	Not an RCT

(Continued)

Cheng 2004	The authors studied other antivirals, included other viral infections and ages of participants were outside protocol age range
Cohen 1976	Ages of participants were outside protocol age range (participants were aged between 20 to 39 years old)
Cohen 2006	It was a study that compared patient access to pharmaceuticals in the UK and US
Dawkins 1968	This study assessed the prophylactic efficacy of an analogue of AMT
Denys 1963	Ages of human participants were outside protocol age range (participants were aged between 19 to 21 years old). Animals were also studied
Dolamore 2003	Case-control study
Dolin 1982	Ages of participants were outside protocol age range (participants were aged between 18 to 45 years old)
Doyle 1998	Ages of participants were outside protocol age range (participants were aged between 18 to 50 years old)
Drinevskii 1998	Randomisation was not stated
Drinka 1998	Groups characteristics not stated. Analyses by age subgroup of interest not available
Enger 2004	Article about oseltamivir
Furuta 2005	It was a study about the mechanism of action of T-705 against influenza virus
Galabov 2006	Non-human trial
Galbraith 1969a	Analyses by age subgroups of interest were not available
Galbraith 1969b	Outcomes of interest were not studied
Galbraith 1971	Analyses by age subgroups of interest were not available
Galbraith 1973	Insufficient data available
Garman 2004	Trial about drugs that inhibit the virus's neuramidase
Gerth 1966	Not an RCT
Griffin 2004	Pharmacological study
Hay 1986	Study about molecular basis resistance of influenza A to amantadine
Hayden 1979	Ages of participants were outside protocol age range
Hayden 1980	Ages of participants were outside protocol age range

(Continued)

Hayden 1981	Ages of participants were outside protocol age range
Hayden 1982	Ages of participants were outside protocol age range
Hayden 1985	Pharmacokinetics study in which ages of participants were outside protocol age range
Hayden 1986	Ages of participants were outside protocol age range
Hayden 1989	Analysis by age subgroups of interest was not available
Hayden 1991	Analysis by age subgroups of interest was not available
Hayden 2000	The drug studied was zanamivir
Hayden 2006	Not a RCT
Hornick 1969	Ages of participants were outside protocol age range
Hout 2006	It is a study about the human immunodeficiency virus
Hout 2006b	It is a study about the human immunodeficiency virus
Hurt 2007	Not an RCT
Ilyushina 2005	Not an RCT
Ilyushina 2006	It was examined if the combined therapy with two classes of anti-influenza drugs could affect the emergence of resistant virus variants in vitro
Ilyushina 2007	Non-human trial
Ilyushina 2007b	Non-human trial
Ison 2006	A case series
Ito 2000	Ages of participants were outside protocol age range
Ito 2006	Study about influenza vaccination
Jefferson 2004	Systematic review about effect and safety of AMT and RMT in healthy adults
Jefferson 2006a	Systematic review about antivirals for influenza in healthy adults
Jones 2006	A trial in which a 20-amino-acid peptide was used
Kantor 1980	Ages of participants were outside protocol age range (participants were aged between 17 to 53 years old)

(Continued)

Kawai 2005	Not an RCT
Khakoo 1981	AMT and/or RMT were not tested in this trial
Kiso 2004	Descriptive study to investigate oseltamivir resistance in children treated for influenza
Kitamoto 1969	Duplicated results
Knight 1969	Ages of participants were outside protocol age range
Knight 1970a	Ages of participants were outside protocol age range
Knight 1970b	Ages of participants were outside protocol age range
Knight 1981	Ribavirin study in which ages of participants were outside protocol age range (participants were aged between 22 to 42 years old)
Krylov 1978	Analysis by age subgroups of interest was not available
Kulichenko 2003	Ages of participants were outside protocol age range
Le Tissier 2005	Non-human trial
Leeming 1969	Insufficient data available
Leone 2005	Article about the use of AMT for traumatic brain injury
Leung 1979	Outcomes of interest were not studied
Lim 2007	A study about an influenza-like illness
Lin 2006	A study about neurologic manifestations in children with influenza B
Linder 2005	The authors measured the rates of antiviral and antibiotic prescribing for patients with influenza
Lipatov 2007	The study was conducted in influenza viruses isolated from poultry
Little 1976	Analyses by age subgroups of interest were not available
Little 1978	Article is about hyperreactivity and airway dysfunction in influenza infection and not about treatment or prevention of influenza
Lutz 2005	It is a study about a method for detecting and quantifying influenza A virus replication
Lynd 2005	Not an RCT
Machado 2004	Article was about the use of oseltamivir to control influenza complications after bone marrow transplantation

(Continued)

Mallia 2007	Not an RCT
Maricich 2004	Not an RCT
Mase 2007	The study was conducted in influenza viruses isolated from poultry
Mate 1970	Ages of participants were outside protocol age range
Mate 1971	Ages of participants were outside protocol age range
Matsuya 2007	A study about the synthesis and evaluation of dihydrofuran-fused perhydrophenanthrenes as a new anti-influenza agent
Matthews 2004	Review article about treatment of viral hepatitis and oncological conditions
McCullers 2004	Non-human trial
McKay 2006	Non-human trial
Mishin 2005	Not a clinical trial
Monto 1979	Ages of participants were outside were outside protocol age (participants were aged between 18 to 24 years old)
Muldoon 1976	Ages of participants were outside protocol age range
Nafta 1970	A wider range of age was considered. Analysis by age subgroups of interest was not available
Natsina 1994	Randomisation was not stated. Additional information not available
O'Donoghute 1973	Analysis by age subgroups of interest was not available
Obrosova-Serova 1972	Study about effectiveness of midantan and interferon inducers as means of non-specific prevention of influenza
Oker-Blom 1970	Ages of participants were outside protocol age range (participants were aged between 20 to 28 years old)
Ong 2007	Not an RCT
Pachucki 2004	Article about a diagnostic test
Peiris 2004	The aim of the authors was not to study AMT and RMT to prevent or treat influenza
Pemberton 1986	Article about AMT resistance in clinical influenza A and virus isolates
Petterson 1980	Insufficient data available
Pritchard 1989	Article about the treatment of juvenile chronic arthritis with antivirals

(Continued)

Quarles 1981	Ages of participants were outside protocol age range
Quilligan 1966	Not an RCT
Rabinovich 1969	Ages of participants were outside protocol age range
Reis 2006	It is an article about neurologic effects of AMT
Reuman 1989a	Ages of participants were outside protocol age range (participants were aged between 18 to 40 years old)
Reuman 1989b	Ages of participants were outside protocol age range (participants were aged between 18 to 55 years old)
Risebrough 2005	Not an RCT
Rose 1980	Not an RCT
Rothberg 2005	Not an RCT
Saito 2006	Not an RCT
Sauerbrei 2006	Not an RCT
Schapira 1971	Analysis by age subgroups of interest was not available
Schmidt 2004	Review article
Sears 1987	Ages of participants were outside protocol age range (participants were aged between 18 to 40 years old)
Semlitsch 1992	The purpose of this article was to study the acute effects of AMT infusions on event-related potentials
Serkedjewa 2007	Non-human trial
Shuler 2007	Case-control study
Shvetsova 1974	The trial authors studied different populations. No information was available about clinical outcomes and confirmation of influenza diagnosis
Skoner 1999	Ages of participants were outside protocol age range (participants were aged between 18 to 50 years old)
Smorodintsev 1970a	Ages of participants were outside protocol age range
Smorodintsev 1970b	Ages of participants were outside protocol age range
Smorodintsev 1970c	Ages of participants were outside protocol age range (participants were aged between 18 to 30 years old)
Somani 1991	Randomisation was not stated. The groups were not similar at baseline

(Continued)

Tajima 2006	It is a study about etiology and treatment in hospitalised children with pneumonia
Takemura 2005	Not a study about influenza A
Terabayashi 2006	The article is about the inhibition of influenza-virus-induced cytopathy by sialyglycoconjugates
Thompson 1987	Insufficient data presented
Togo 1968	Ages of participants were outside protocol age range
Togo 1970	Ages of participants were outside protocol age range
Togo 1972	The drug studied was cyclooctylamine
Townsend 2006	Not an RCT
van der Wouden 2005	Not an RCT
Van Voris 1981	Ages of participants were outside protocol age range
Van Voris 1985	Study about four antibody techniques to assess influenza infection
Webster 1986	Non-human trial
Wendel 1966	Ages of participants were outside protocol age range (participants were aged between 17 to 54 years old)
Wingfield 1969	Ages of participants were outside protocol age range
Wong 2006	Not an RCT
Wright 1976	Analysis by age subgroups of interest was not available
Wultzler 2004	Not a clinical trial
Yamaura 2003	The studied antiviral was oseltamivir
Younkin 1983	Ages of participants were outside protocol age range (participants were aged between 17 to 20 years old)
Yuen 2005	Not an RCT
Zeuzem 1999	The purpose of the authors was to study treatment for chronic hepatitis C

AMT: amantadine

RMT: rimantadine

PB: placebo

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. AMT and RMT compared to control in the treatment of influenza A in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever day 3	3	173	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.20, 0.79]
1.1 AMT	2	104	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.08, 1.75]
1.2 RMT	1	69	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.14, 0.91]
2 Cough day 7	1	69	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.63, 1.10]
2.1 RMT	1	69	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.63, 1.10]
3 Malaise day 6	1	69	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.63, 1.70]
3.1 RMT	1	69	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.63, 1.70]
4 Conjunctivitis day 5	1	69	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.01, 3.49]
4.1 RMT	1	69	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.01, 3.49]
5 Eye symptoms day 5 (pain on movement and visual distortion)	1	69	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.10, 3.24]
5.1 RMT	1	69	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.10, 3.24]

Comparison 2. AMT and RMT compared to control in the prophylaxis of influenza A in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infection	5	951	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.09, 0.66]
1.1 AMT	2	773	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.04, 0.30]
1.2 RMT	3	178	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.21, 1.15]

Comparison 3. Adverse effects of AMT and RMT compared to control in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea	3	655	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.42, 1.47]
1.1 AMT	2	599	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.43, 1.53]
1.2 RMT	1	56	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.02, 8.41]
2 Exanthema	2	599	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.21, 2.34]
2.1 AMT	2	599	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.21, 2.34]
3 Malaise	2	599	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.41, 1.96]
3.1 AMT	2	599	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.41, 1.96]

4 Muscular, limb pain	2	599	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.46, 1.59]
4.1 AMT	2	599	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.46, 1.59]
5 Headache	2	599	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.52, 1.03]
5.1 AMT	2	599	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.52, 1.03]
6 Dyspnoea	1	159	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.02, 9.02]
6.1 AMT	1	159	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.02, 9.02]
7 Gastrointestinal symptoms	1	76	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.08, 18.05]
7.1 RMT	1	76	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.08, 18.05]
8 Dizziness	3	655	Risk Ratio (M-H, Random, 95% CI)	4.69 [0.53, 41.75]
8.1 AMT	2	599	Risk Ratio (M-H, Random, 95% CI)	6.63 [0.32, 137.33]
8.2 RMT	1	56	Risk Ratio (M-H, Random, 95% CI)	3.21 [0.14, 75.68]
9 Central nervous system symptoms	1	76	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.01, 4.70]
9.1 RMT	1	76	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.01, 4.70]
10 Change in behaviour	1	76	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.01, 4.70]
10.1 RMT	1	76	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.01, 4.70]
11 Stimulation/ insomnia	2	599	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.12, 1.74]
11.1 AMT	2	599	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.12, 1.74]
12 Cerebelar ataxia	1	69	Risk Ratio (M-H, Random, 95% CI)	2.61 [0.11, 61.80]
12.1 RMT	1	69	Risk Ratio (M-H, Random, 95% CI)	2.61 [0.11, 61.80]
13 Hyperreactivity	1	56	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.02, 8.41]
13.1 RMT	1	56	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.02, 8.41]
14 Tinnitus	1	56	Risk Ratio (M-H, Random, 95% CI)	3.21 [0.14, 75.68]
14.1 RMT	1	56	Risk Ratio (M-H, Random, 95% CI)	3.21 [0.14, 75.68]
15 Nausea/ vomiting	4	724	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.24, 1.58]
15.1 AMT	2	599	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.15, 2.00]
15.2 RMT	2	125	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.10, 9.01]
16 Arrythmia	2	599	Risk Ratio (M-H, Random, 95% CI)	Not estimable
16.1 AMT	2	599	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Comparison 4. AMT and RMT compared to control in the prophylaxis of influenza A in the elderly

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 RMT (proved and clinical infection)	3	191	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.13, 4.07]
2 RMT 200	2	75	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.12, 1.63]
3 RMT 100	2	130	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.10, 21.10]
4 RMT Monto (100 + 200) and Patriarca	2	103	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.14, 1.41]

Comparison 5. Adverse effects of AMT and RMT compared to control in the elderly

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache	1	198	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.21, 3.38]
1.1 RMT	1	198	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.21, 3.38]
2 Stimulation/ insomnia	2	233	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.43, 6.02]
2.1 RMT	2	233	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.43, 6.02]
3 Dizziness	1	35	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.15, 5.97]
3.1 RMT	1	35	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.15, 5.97]
4 Anxiety	1	35	Risk Ratio (M-H, Random, 95% CI)	2.83 [0.92, 8.74]
4.1 RMT	1	35	Risk Ratio (M-H, Random, 95% CI)	2.83 [0.92, 8.74]
5 Confusion	2	233	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.40, 1.56]
5.1 RMT	2	233	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.40, 1.56]
6 Fatigue	2	233	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.41, 1.60]
6.1 RMT	2	233	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.41, 1.60]
7 Nausea	2	233	Risk Ratio (M-H, Random, 95% CI)	1.99 [0.45, 8.75]
7.1 RMT	2	233	Risk Ratio (M-H, Random, 95% CI)	1.99 [0.45, 8.75]
8 Depression	2	233	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.53, 4.98]
8.1 RMT	2	233	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.53, 4.98]
9 Impaired concentration	1	198	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.10, 2.41]
9.1 RMT	1	198	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.10, 2.41]
10 Loss of appetite	2	233	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.56, 2.17]
10.1 RMT	2	233	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.56, 2.17]
11 Rash or allergic reaction	1	198	Risk Ratio (M-H, Random, 95% CI)	3.53 [0.18, 67.28]
11.1 RMT	1	198	Risk Ratio (M-H, Random, 95% CI)	3.53 [0.18, 67.28]
12 Seizures or clonic twitching	1	198	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.23, 17.54]
12.1 RMT	1	198	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.23, 17.54]
13 Dry mouth	1	198	Risk Ratio (M-H, Random, 95% CI)	0.7 [0.23, 2.12]
13.1 RMT	1	198	Risk Ratio (M-H, Random, 95% CI)	0.7 [0.23, 2.12]
14 Vomiting	2	233	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.38, 2.60]
14.1 RMT	2	233	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.38, 2.60]

Comparison 6. Use of different doses of AMT and RMT for prophylaxis and treatment of influenza A in the elderly

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical and laboratorial infection	1	54	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.21, 4.20]
1.1 RMT	1	54	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.21, 4.20]

Comparison 7. Adverse effects related to different doses of AMT and RMT in the elderly

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Confusion	1	262	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.41, 1.65]
1.1 RMT	1	262	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.41, 1.65]
2 Depression	1	262	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.12, 1.65]
2.1 RMT	1	262	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.12, 1.65]
3 Impaired concentration	1	262	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.11, 3.98]
3.1 RMT	1	262	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.11, 3.98]
4 Insomnia or sleeplessness	1	262	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.26, 3.97]
4.1 RMT	1	262	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.26, 3.97]
5 Loss of appetite	1	262	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.27, 1.46]
5.1 RMT	1	262	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.27, 1.46]
6 Rash or allergic reaction	1	262	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.04, 3.21]
6.1 RMT	1	262	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.04, 3.21]
7 Seizure or clonic twitching	1	262	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 2.07]
7.1 RMT	1	262	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 2.07]
8 Dry mouth	1	262	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.43, 3.11]
8.1 RMT	1	262	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.43, 3.11]
9 Fatigue and drowsiness	1	262	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.45, 2.87]
9.1 RMT	1	262	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.45, 2.87]
10 Headache	1	262	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.30, 3.42]
10.1 RMT	1	262	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.30, 3.42]
11 Body weakness or debility	1	262	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.38, 2.18]
11.1 RMT	1	262	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.38, 2.18]

Comparison 8. AMT and RMT compared to other antivirals in the elderly

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 RMT and zanamivir	2	545	Risk Ratio (M-H, Random, 95% CI)	4.63 [1.46, 14.72]

Comparison 9. Additional comparison: RMT compared to control in the prophylaxis of influenza A in children and the elderly

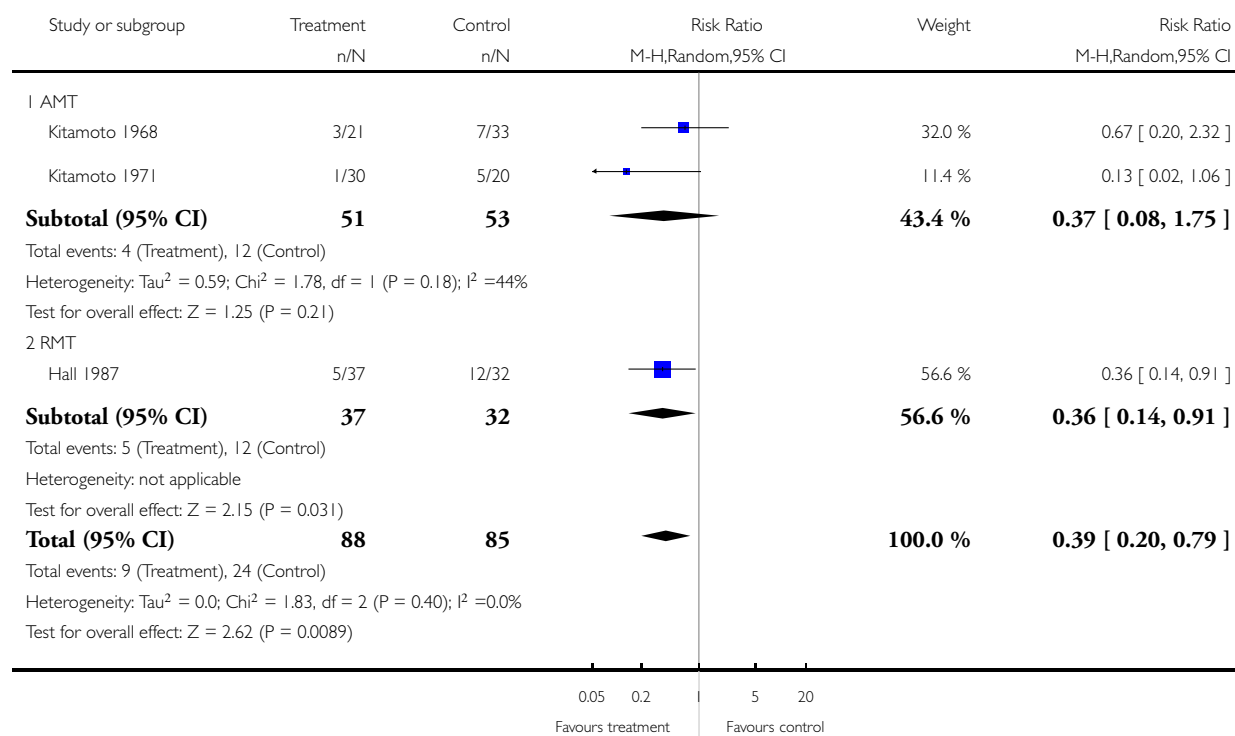
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infection	5	281	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.27, 0.92]
1.1 RMT	5	281	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.27, 0.92]

Analysis 1.1. Comparison 1 AMT and RMT compared to control in the treatment of influenza A in children, Outcome 1 Fever day 3.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 1 AMT and RMT compared to control in the treatment of influenza A in children

Outcome: 1 Fever day 3

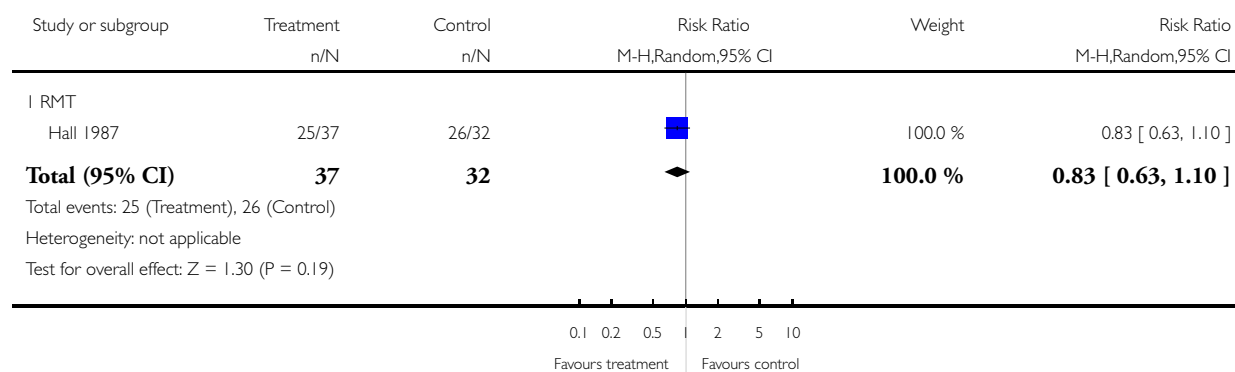


Analysis 1.2. Comparison 1 AMT and RMT compared to control in the treatment of influenza A in children, Outcome 2 Cough day 7.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 1 AMT and RMT compared to control in the treatment of influenza A in children

Outcome: 2 Cough day 7

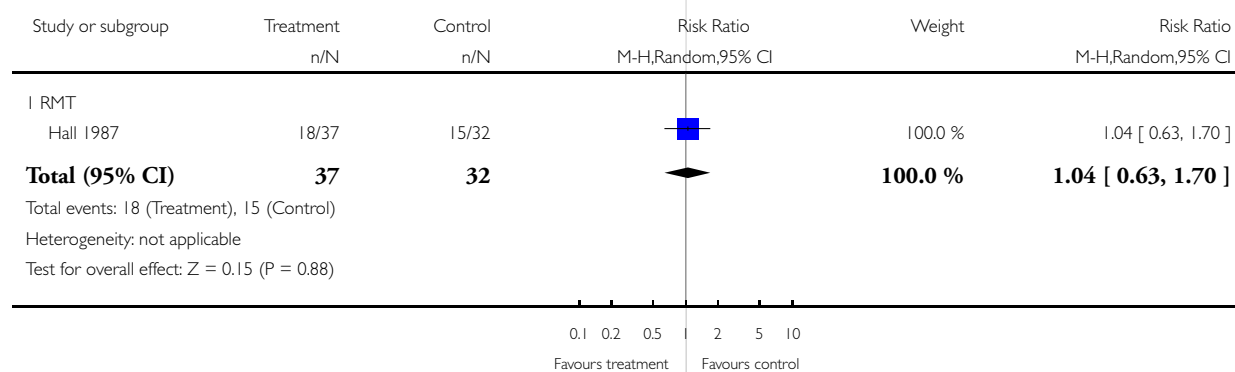


Analysis 1.3. Comparison 1 AMT and RMT compared to control in the treatment of influenza A in children, Outcome 3 Malaise day 6.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 1 AMT and RMT compared to control in the treatment of influenza A in children

Outcome: 3 Malaise day 6

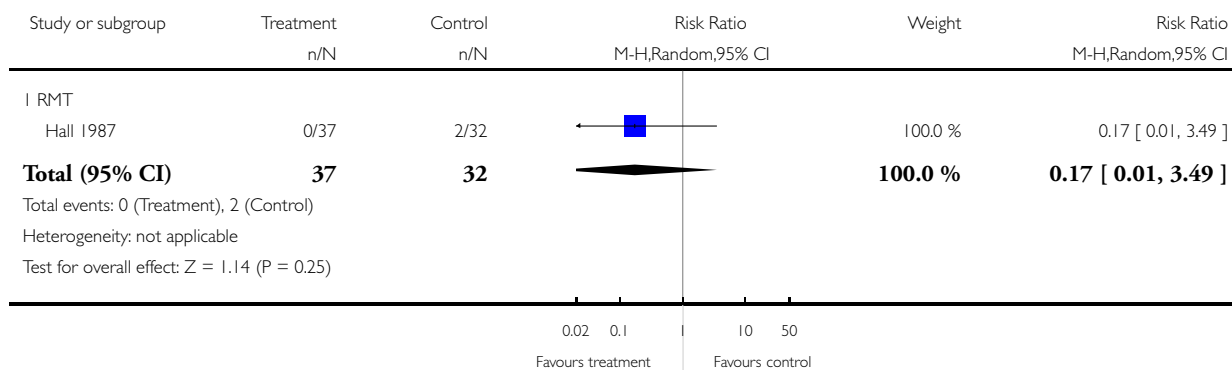


Analysis 1.4. Comparison 1 AMT and RMT compared to control in the treatment of influenza A in children, Outcome 4 Conjunctivitis day 5.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 1 AMT and RMT compared to control in the treatment of influenza A in children

Outcome: 4 Conjunctivitis day 5

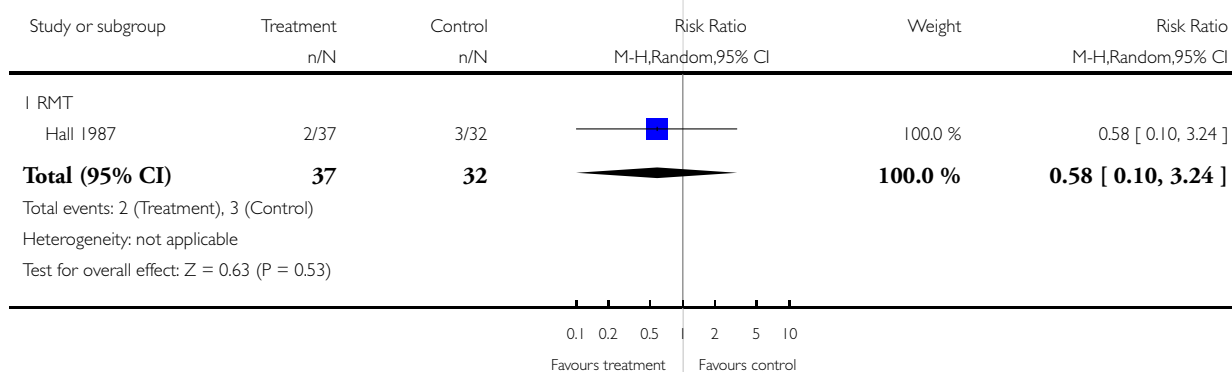


Analysis 1.5. Comparison 1 AMT and RMT compared to control in the treatment of influenza A in children, Outcome 5 Eye symptoms day 5 (pain on movement and visual distortion).

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 1 AMT and RMT compared to control in the treatment of influenza A in children

Outcome: 5 Eye symptoms day 5 (pain on movement and visual distortion)

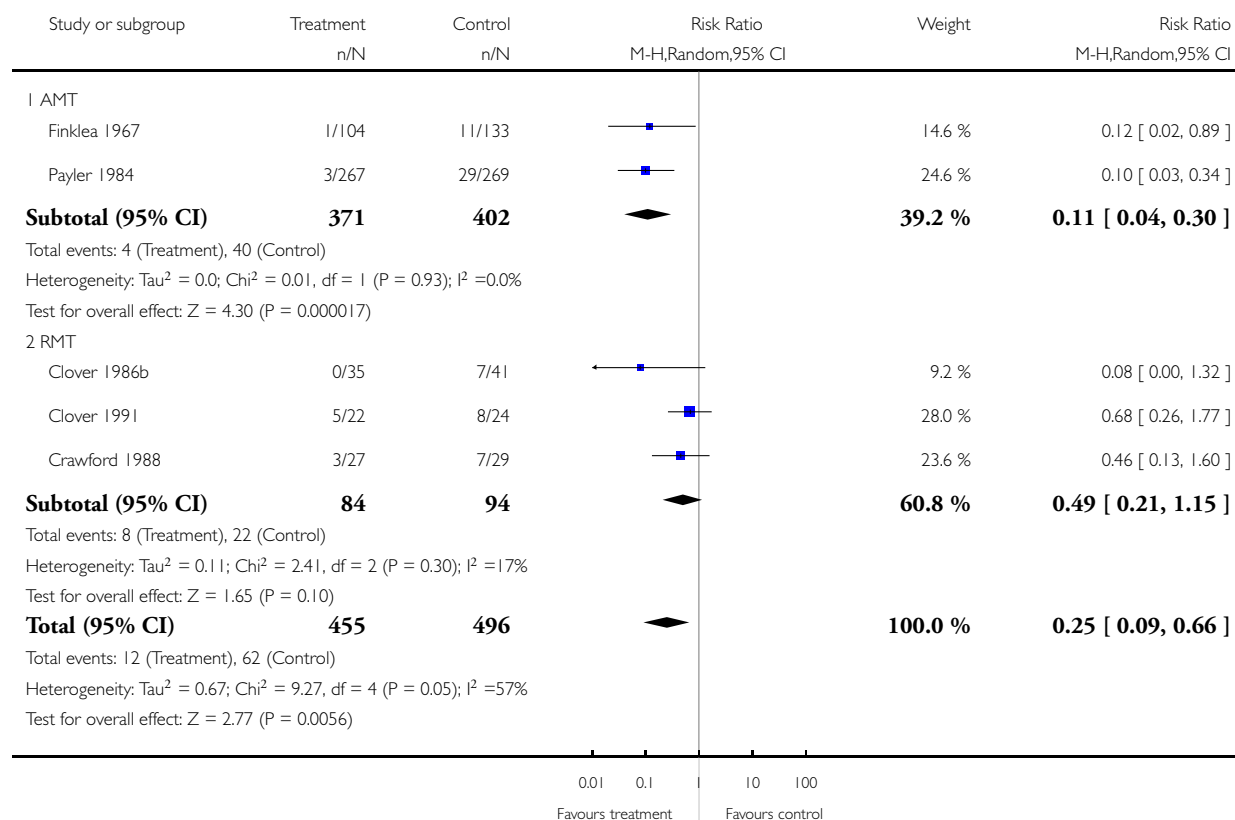


Analysis 2.1. Comparison 2 AMT and RMT compared to control in the prophylaxis of influenza A in children, Outcome 1 Infection.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 2 AMT and RMT compared to control in the prophylaxis of influenza A in children

Outcome: 1 Infection

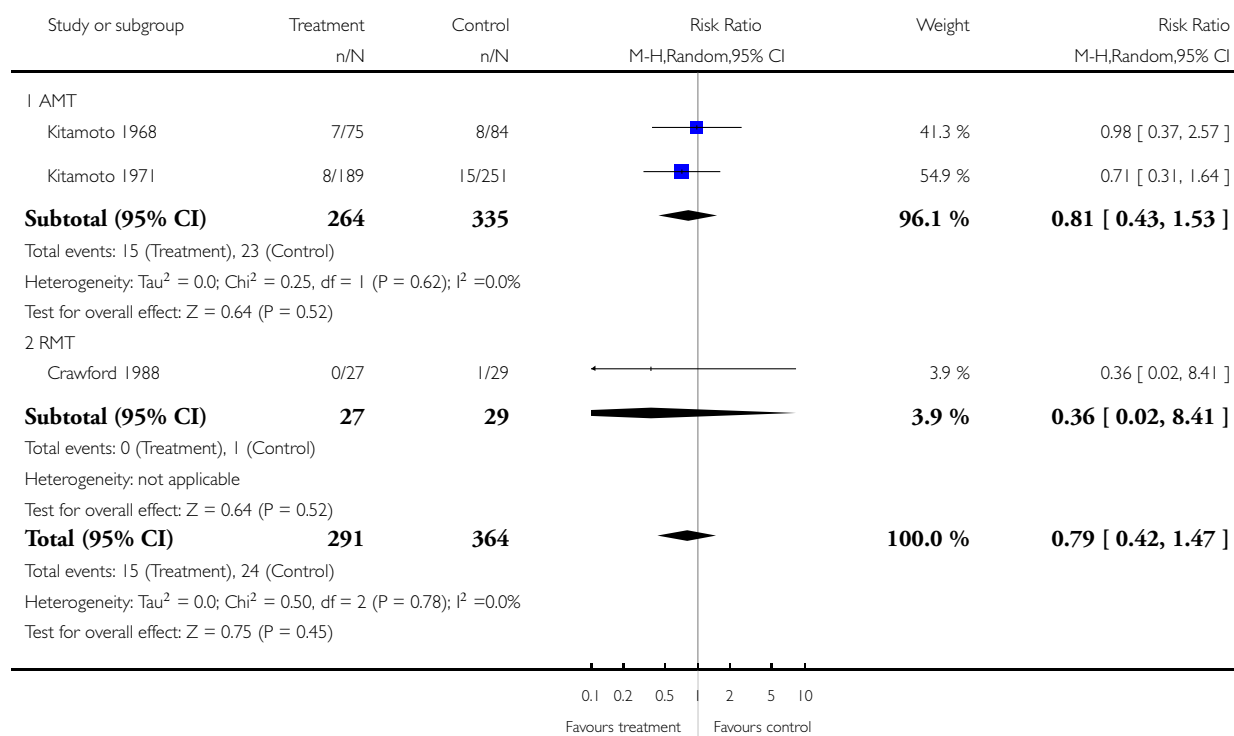


Analysis 3.1. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 1 Diarrhoea.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 1 Diarrhoea

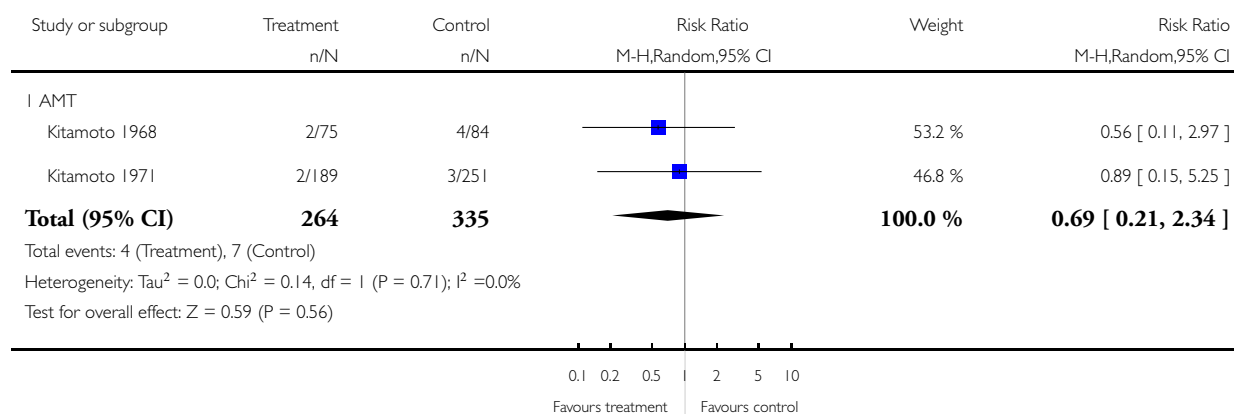


Analysis 3.2. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 2 Exanthema.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 2 Exanthema

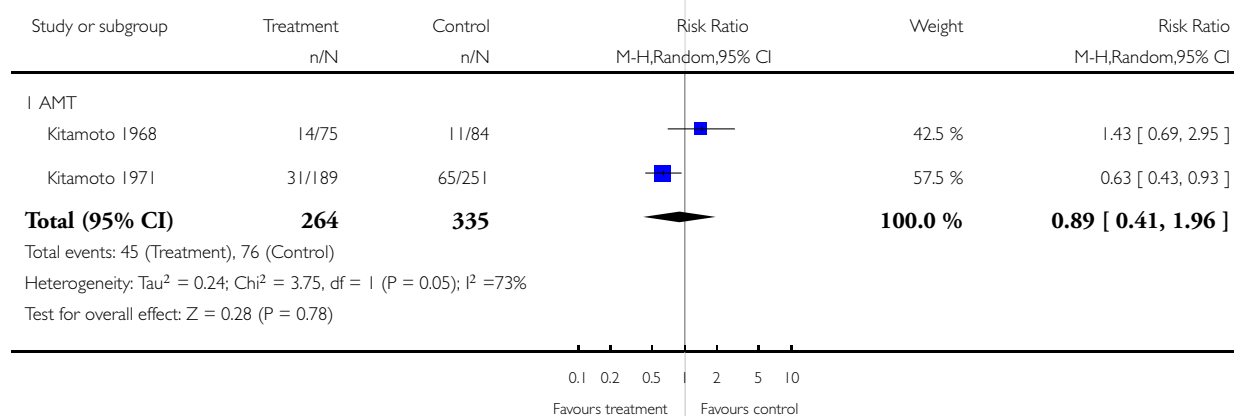


Analysis 3.3. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 3 Malaise.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 3 Malaise

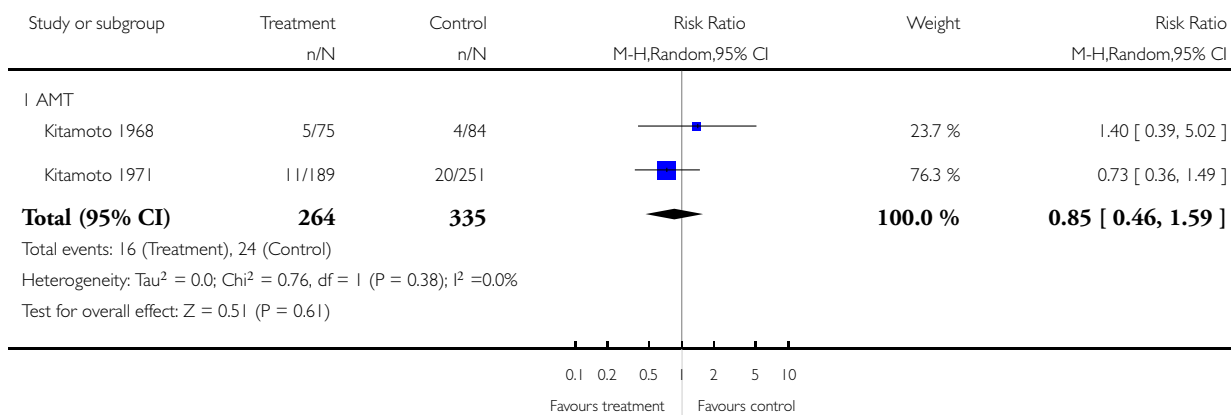


Analysis 3.4. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 4 Muscular, limb pain.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 4 Muscular, limb pain

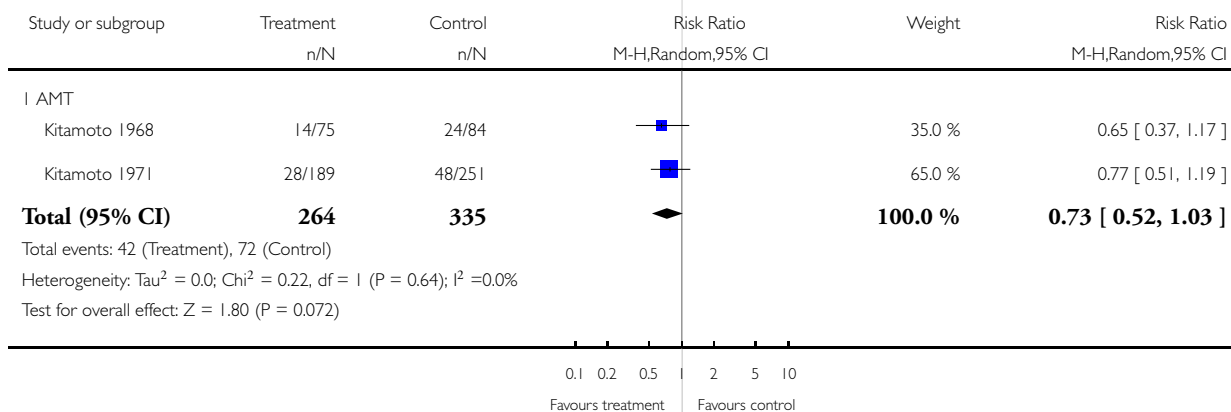


Analysis 3.5. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 5 Headache.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 5 Headache

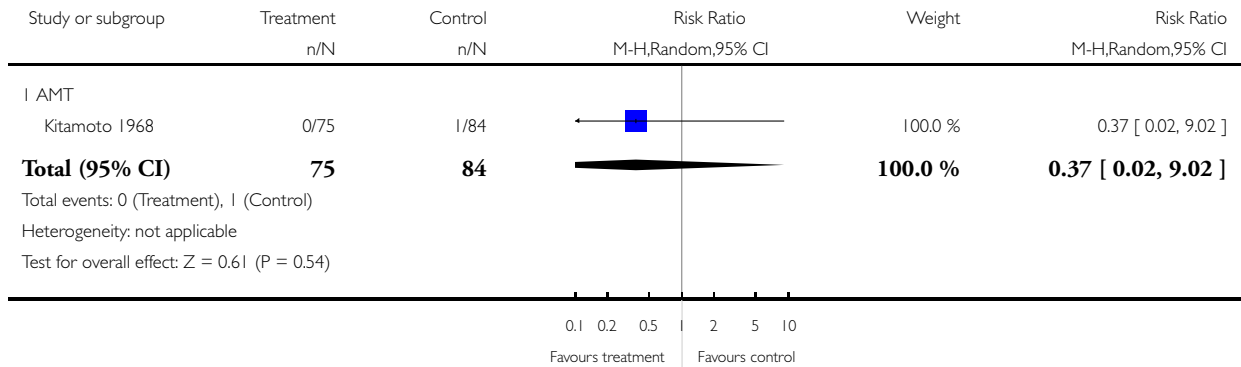


Analysis 3.6. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 6 Dyspnoea.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 6 Dyspnoea

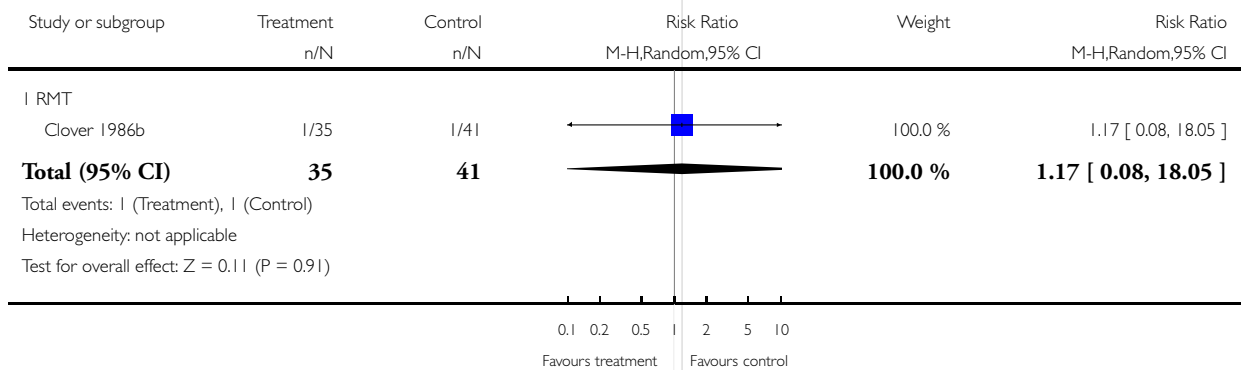


Analysis 3.7. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 7 Gastrointestinal symptoms.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 7 Gastrointestinal symptoms

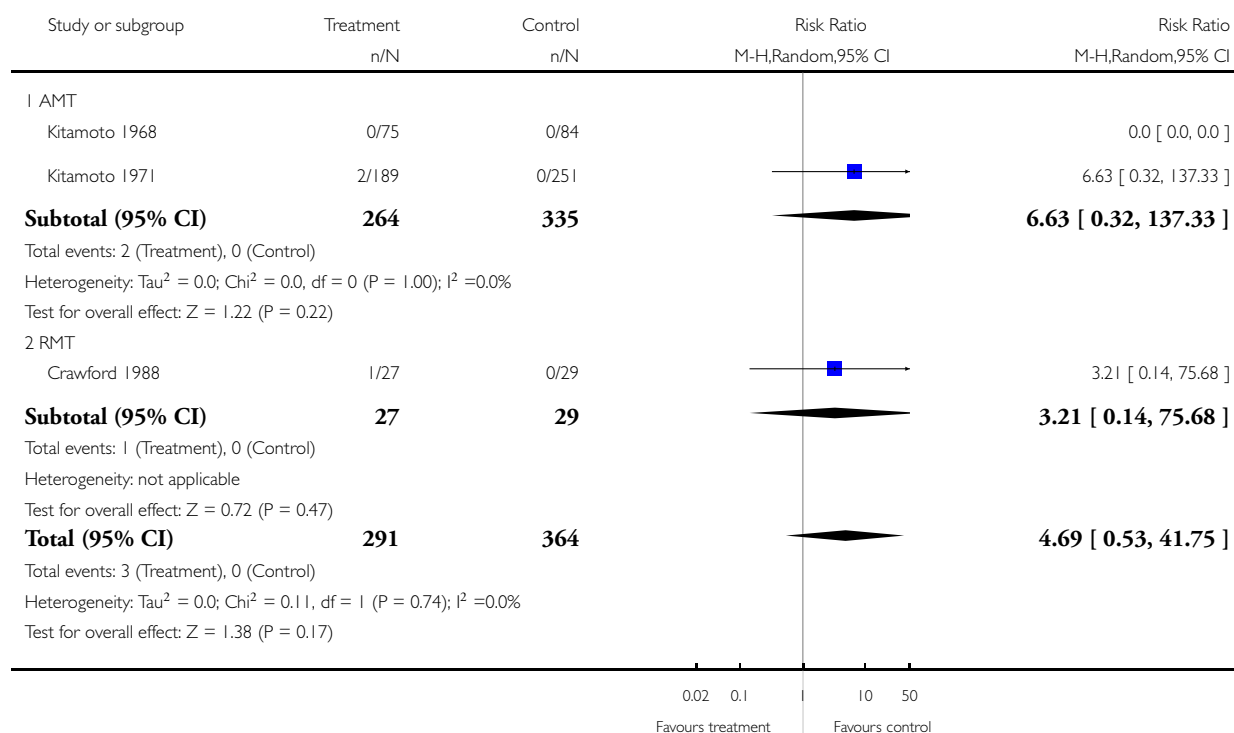


Analysis 3.8. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 8 Dizziness.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 8 Dizziness

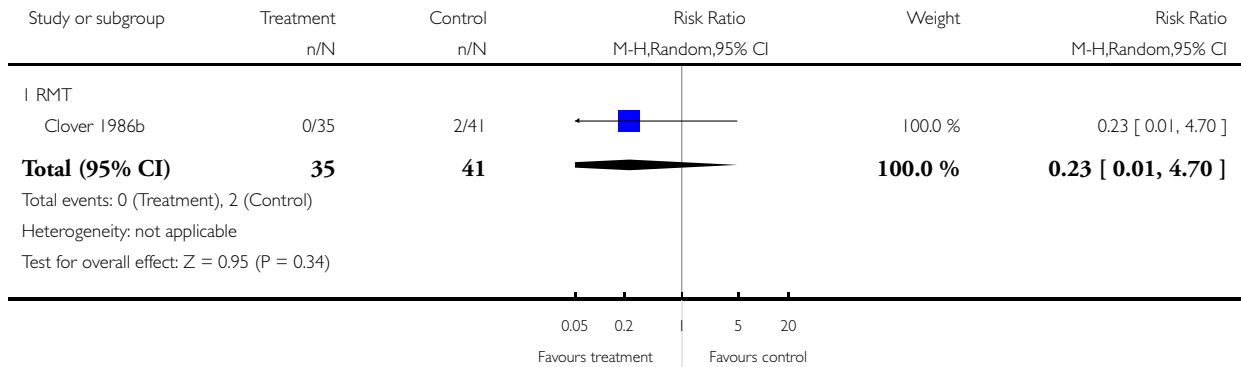


Analysis 3.9. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 9 Central nervous system symptoms.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 9 Central nervous system symptoms

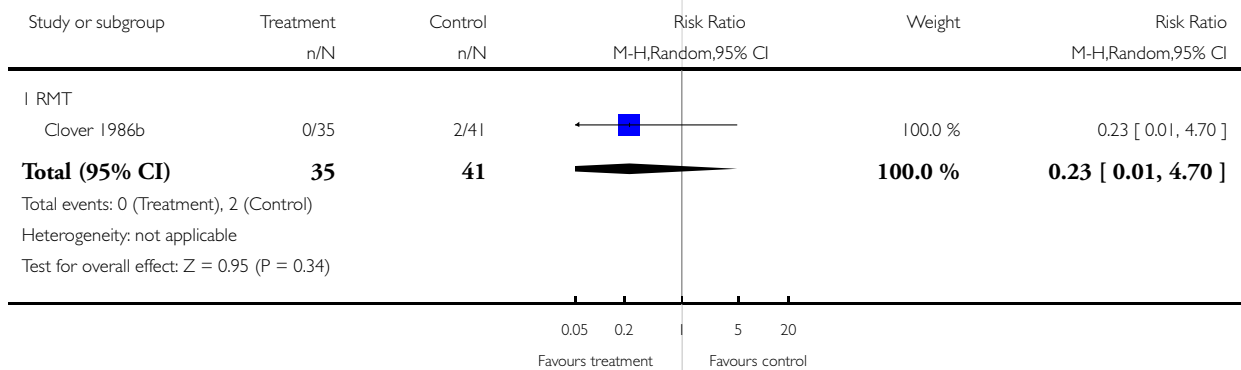


Analysis 3.10. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 10 Change in behaviour.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 10 Change in behaviour

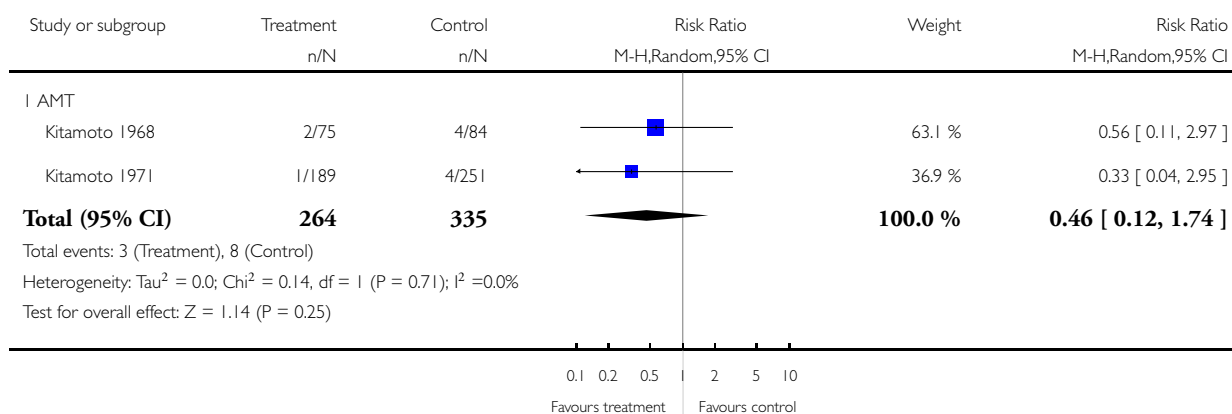


Analysis 3.11. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 11 Stimulation/ insomnia.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 11 Stimulation/ insomnia

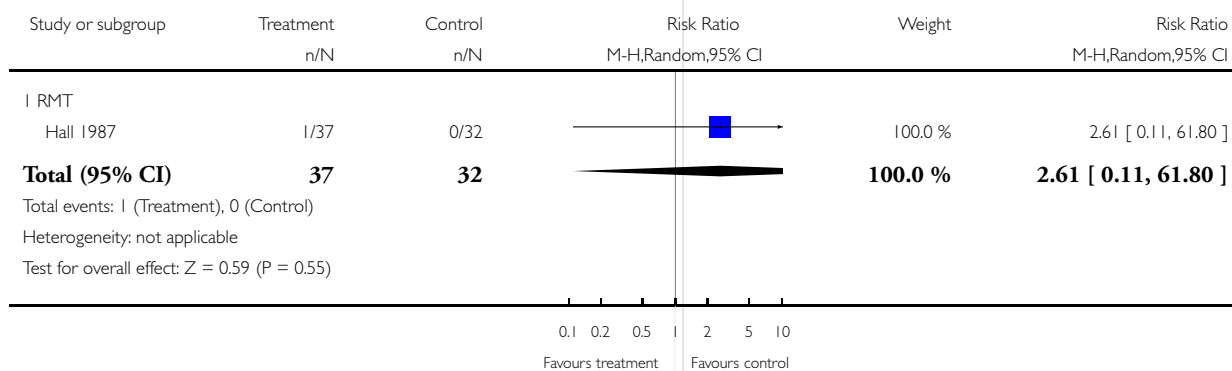


Analysis 3.12. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 12 Cerebellar ataxia.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 12 Cerebellar ataxia

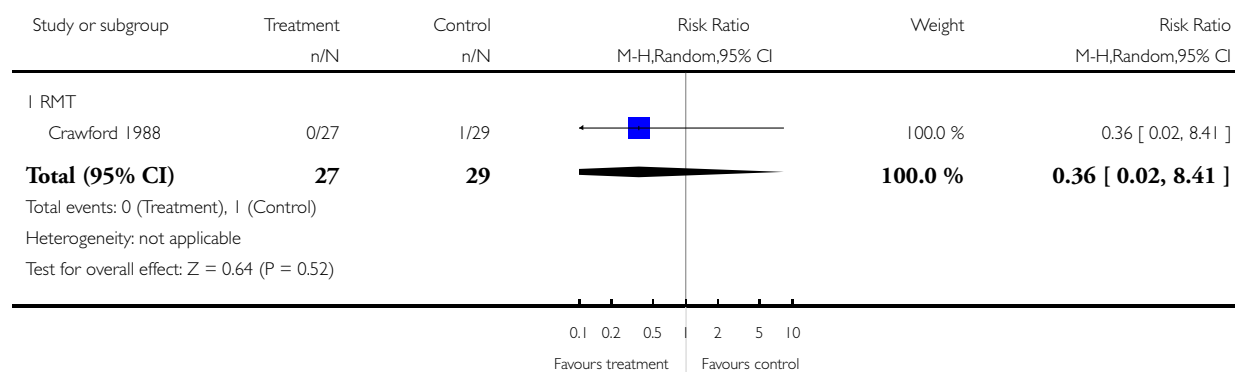


Analysis 3.13. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 13 Hyperreactivity.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 13 Hyperreactivity

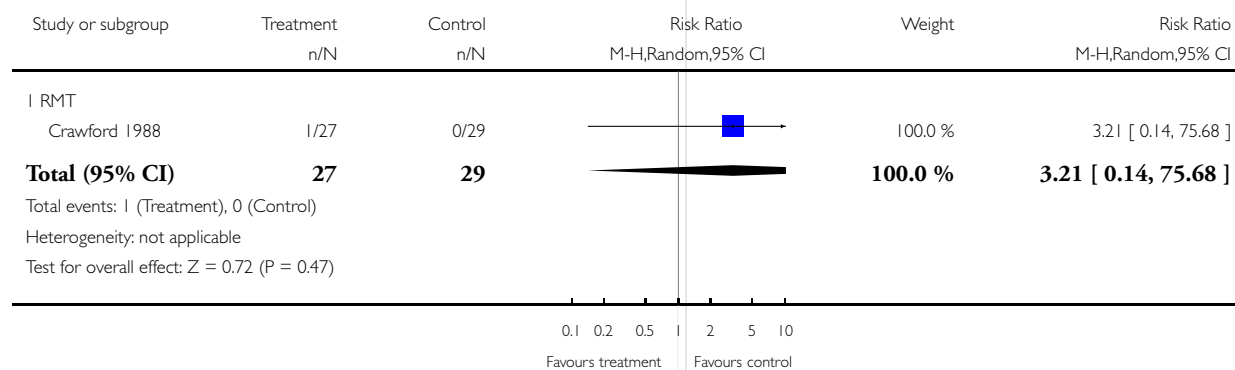


Analysis 3.14. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 14 Tinnitus.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 14 Tinnitus

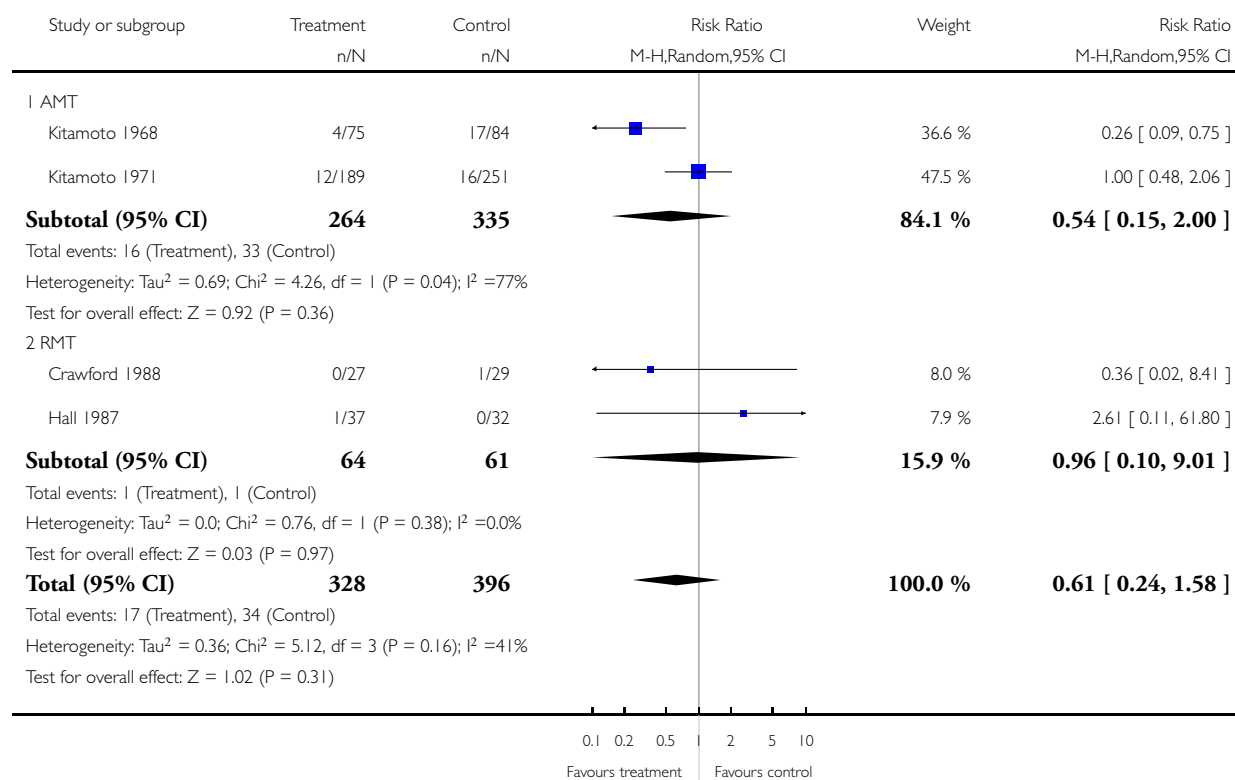


Analysis 3.15. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 15 Nausea/ vomiting.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 15 Nausea/ vomiting

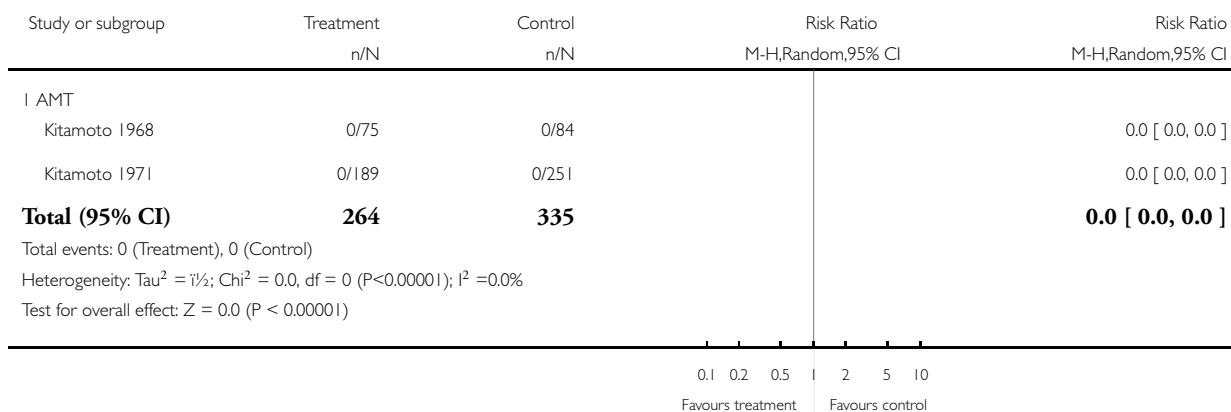


Analysis 3.16. Comparison 3 Adverse effects of AMT and RMT compared to control in children, Outcome 16 Arrhythmia.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 3 Adverse effects of AMT and RMT compared to control in children

Outcome: 16 Arrhythmia

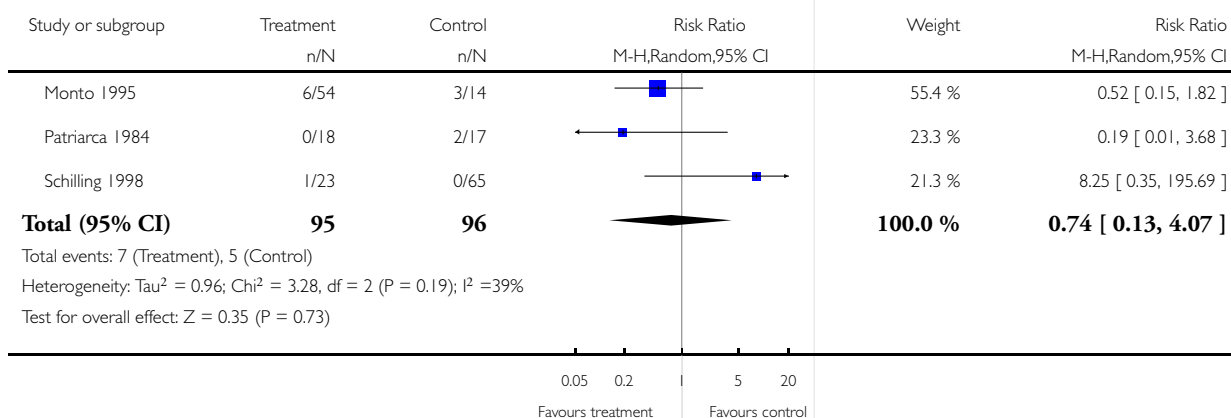


Analysis 4.1. Comparison 4 AMT and RMT compared to control in the prophylaxis of influenza A in the elderly, Outcome 1 RMT (proved and clinical infection).

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 4 AMT and RMT compared to control in the prophylaxis of influenza A in the elderly

Outcome: 1 RMT (proved and clinical infection)

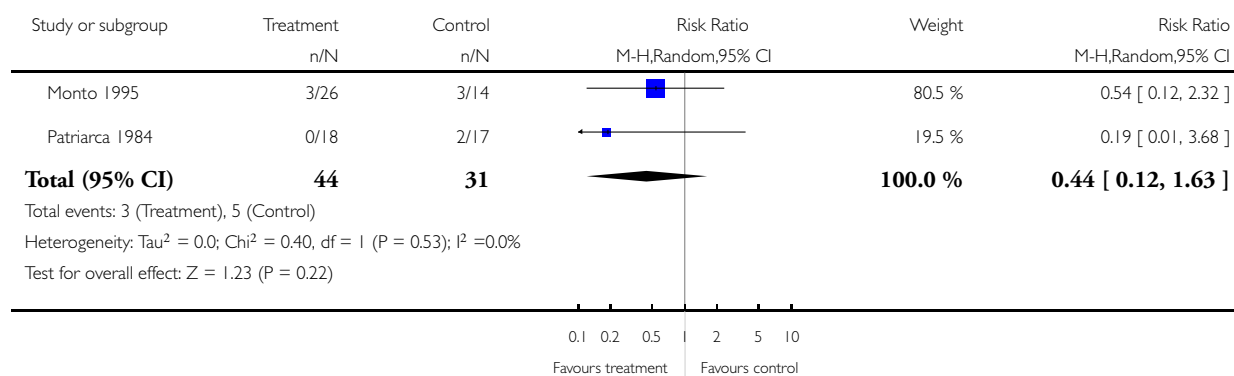


Analysis 4.2. Comparison 4 AMT and RMT compared to control in the prophylaxis of influenza A in the elderly, Outcome 2 RMT 200.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 4 AMT and RMT compared to control in the prophylaxis of influenza A in the elderly

Outcome: 2 RMT 200

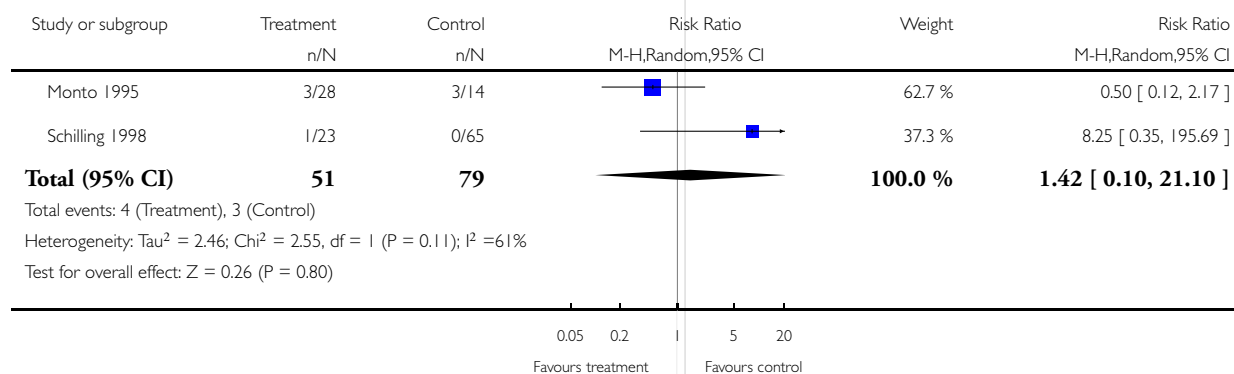


Analysis 4.3. Comparison 4 AMT and RMT compared to control in the prophylaxis of influenza A in the elderly, Outcome 3 RMT 100.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 4 AMT and RMT compared to control in the prophylaxis of influenza A in the elderly

Outcome: 3 RMT 100

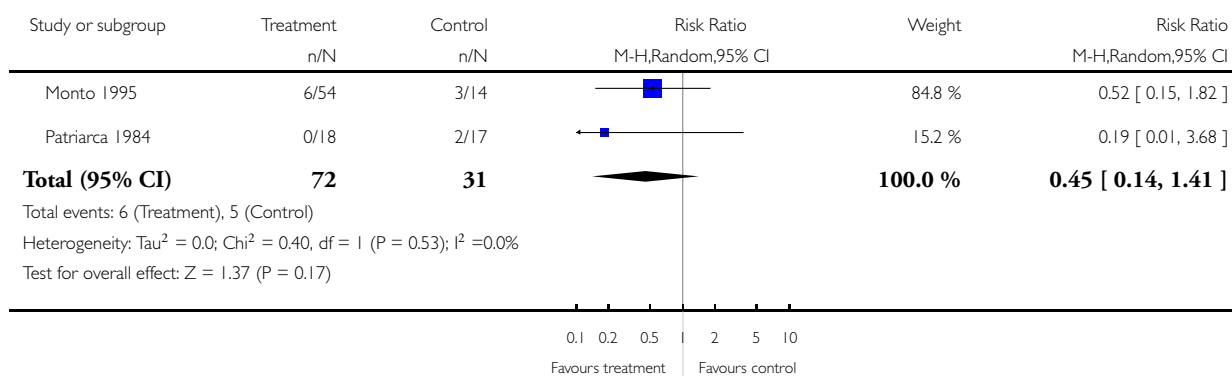


Analysis 4.4. Comparison 4 AMT and RMT compared to control in the prophylaxis of influenza A in the elderly, Outcome 4 RMT Monto (100 + 200) and Patriarca.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 4 AMT and RMT compared to control in the prophylaxis of influenza A in the elderly

Outcome: 4 RMT Monto (100 + 200) and Patriarca

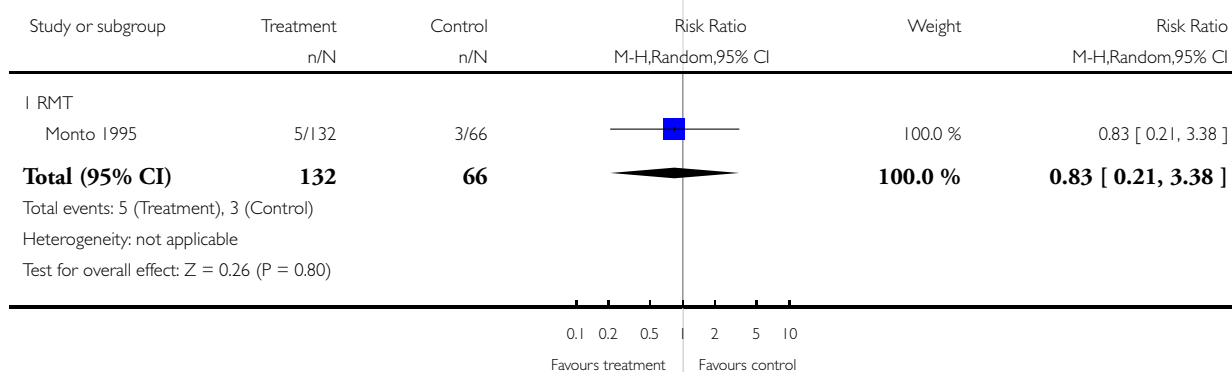


Analysis 5.1. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 1 Headache.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 1 Headache

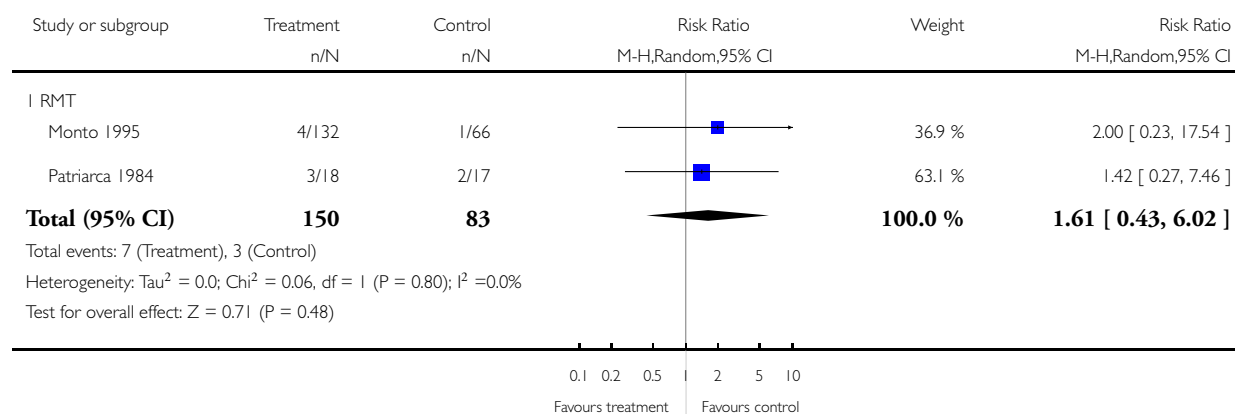


Analysis 5.2. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 2 Stimulation/ insomnia.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 2 Stimulation/ insomnia

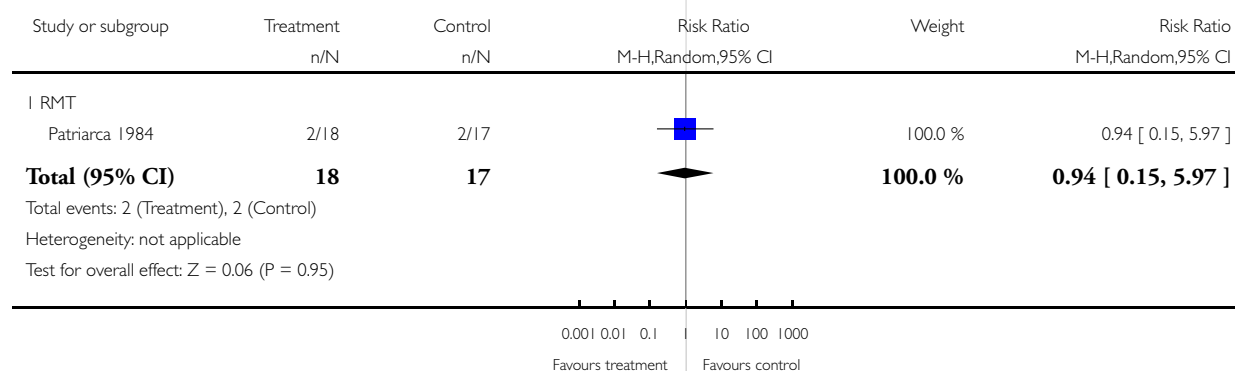


Analysis 5.3. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 3 Dizziness.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 3 Dizziness

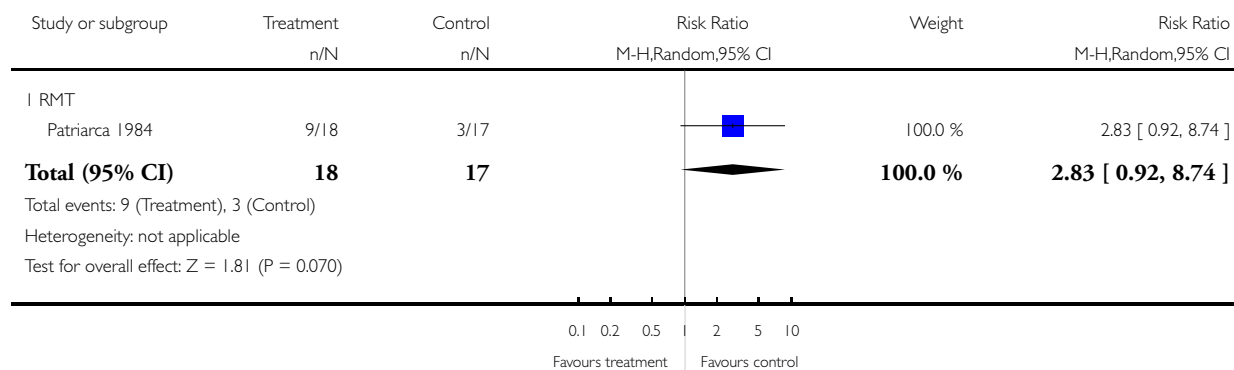


Analysis 5.4. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 4 Anxiety.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 4 Anxiety

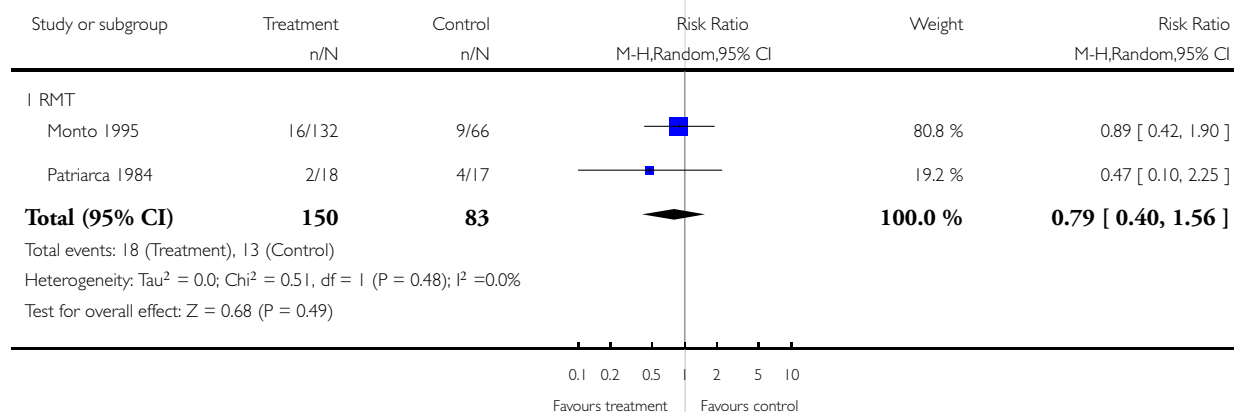


Analysis 5.5. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 5 Confusion.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 5 Confusion

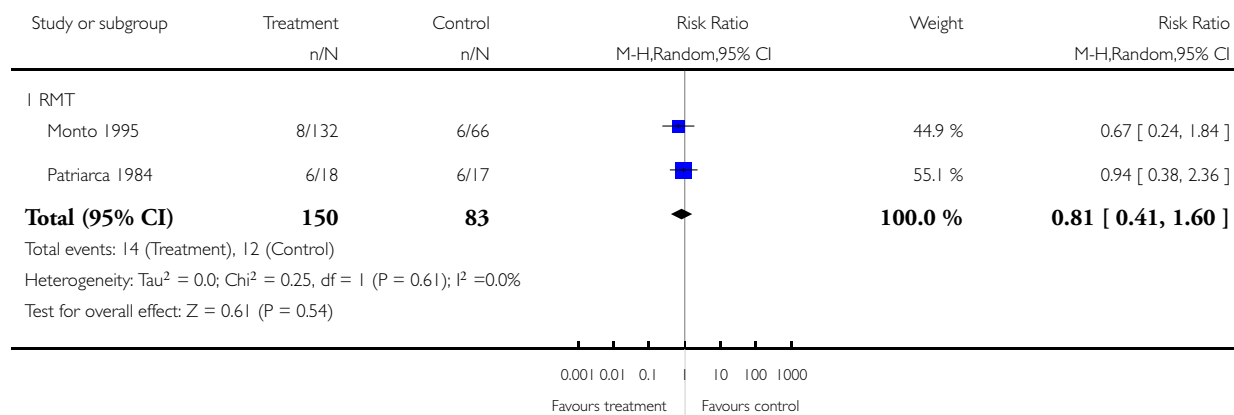


Analysis 5.6. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 6 Fatigue.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 6 Fatigue

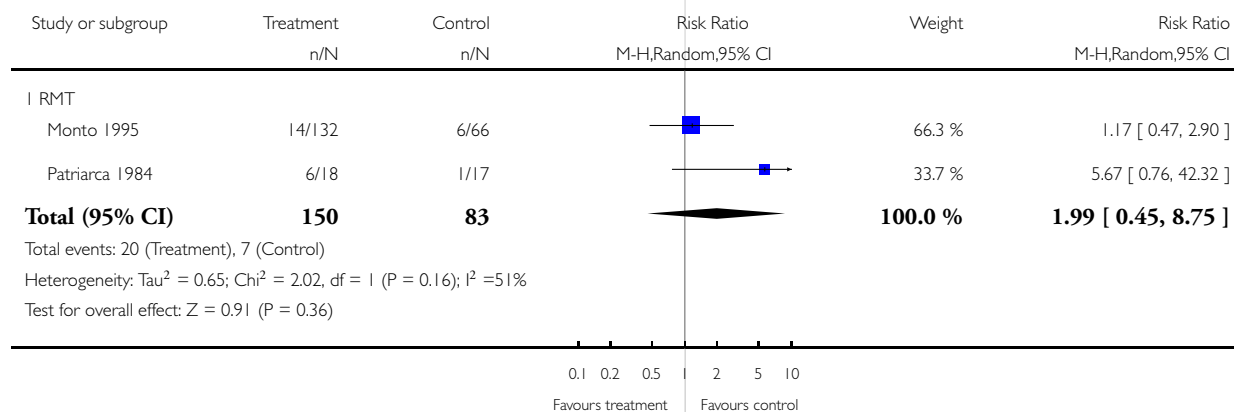


Analysis 5.7. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 7 Nausea.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 7 Nausea

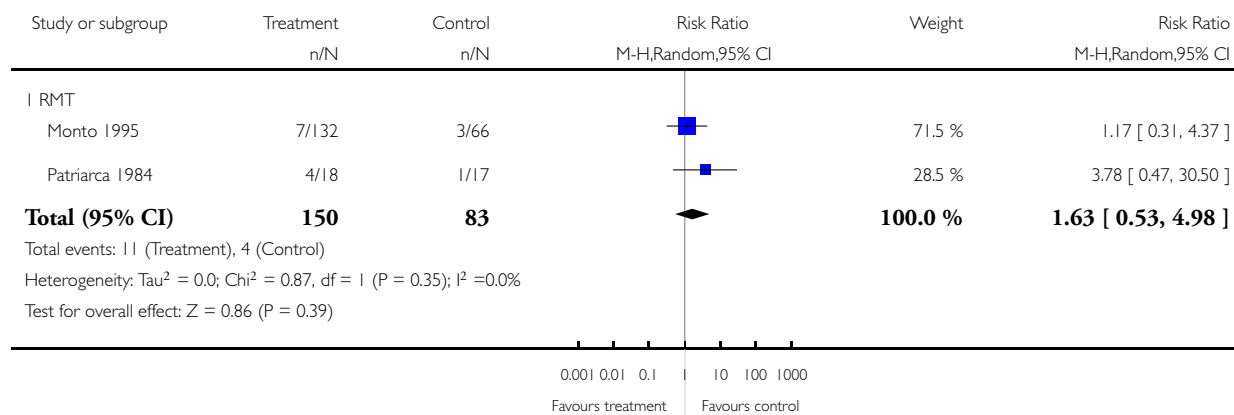


Analysis 5.8. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 8 Depression.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 8 Depression

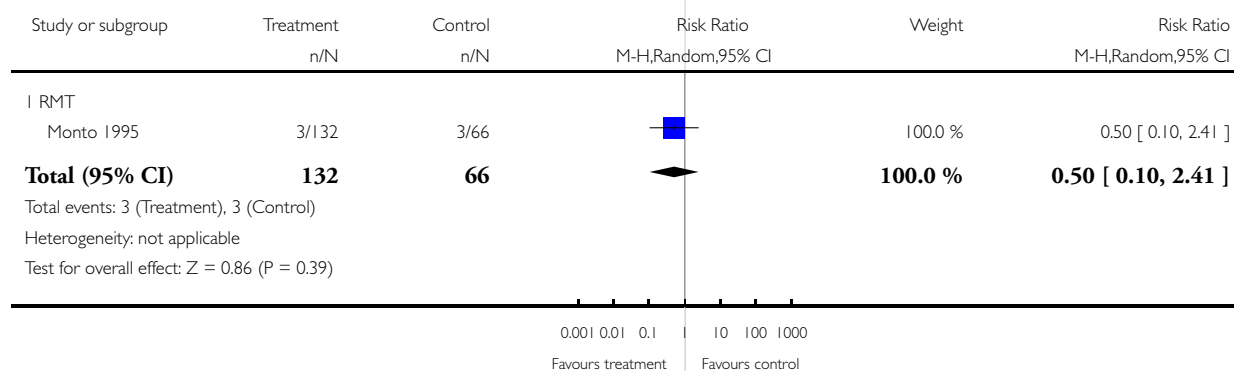


Analysis 5.9. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 9 Impaired concentration.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 9 Impaired concentration

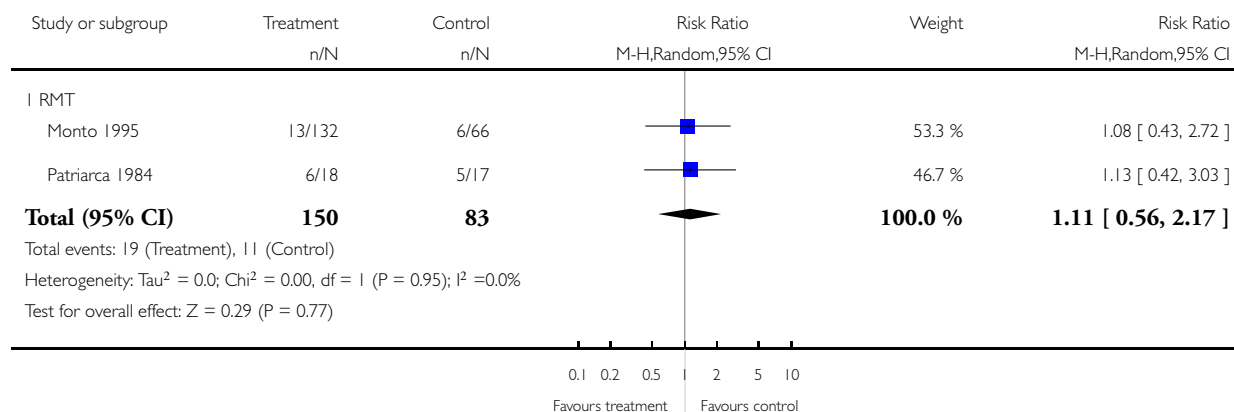


Analysis 5.10. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 10 Loss of appetite.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 10 Loss of appetite

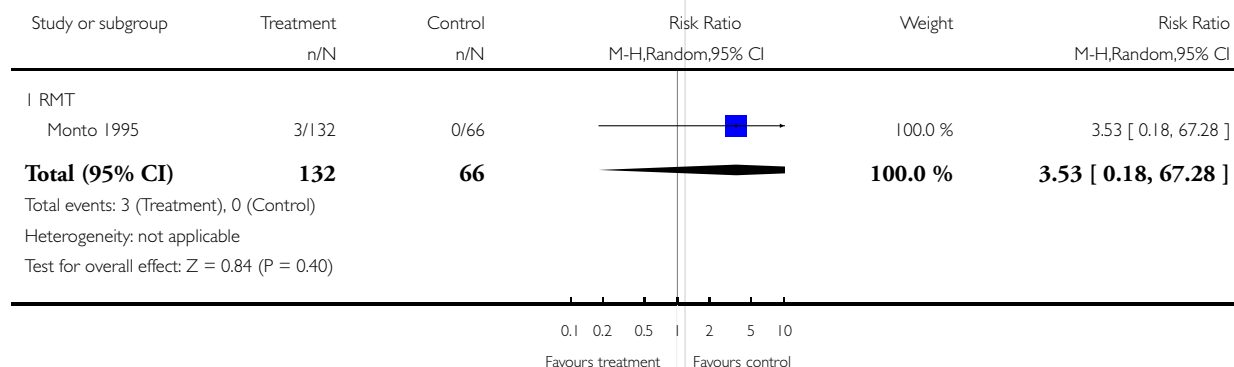


Analysis 5.11. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 11 Rash or allergic reaction.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 11 Rash or allergic reaction

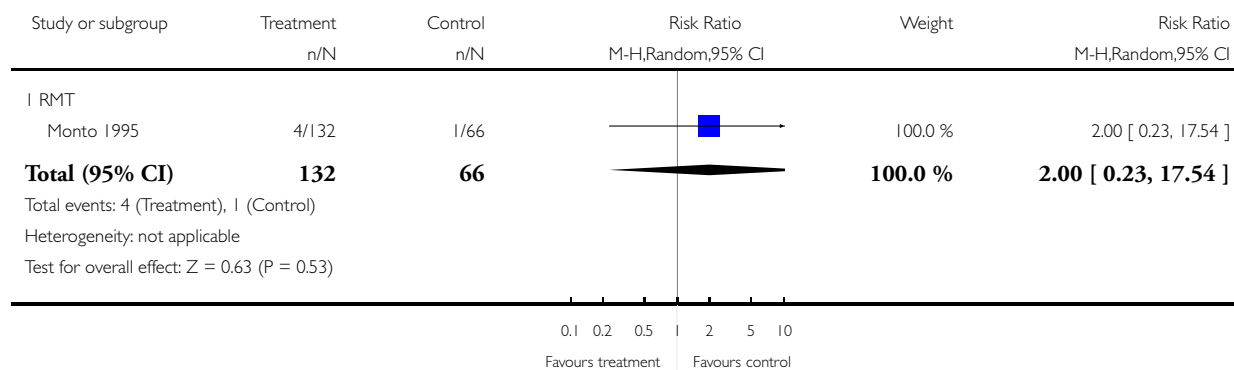


Analysis 5.12. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 12 Seizures or clonic twitching.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 12 Seizures or clonic twitching

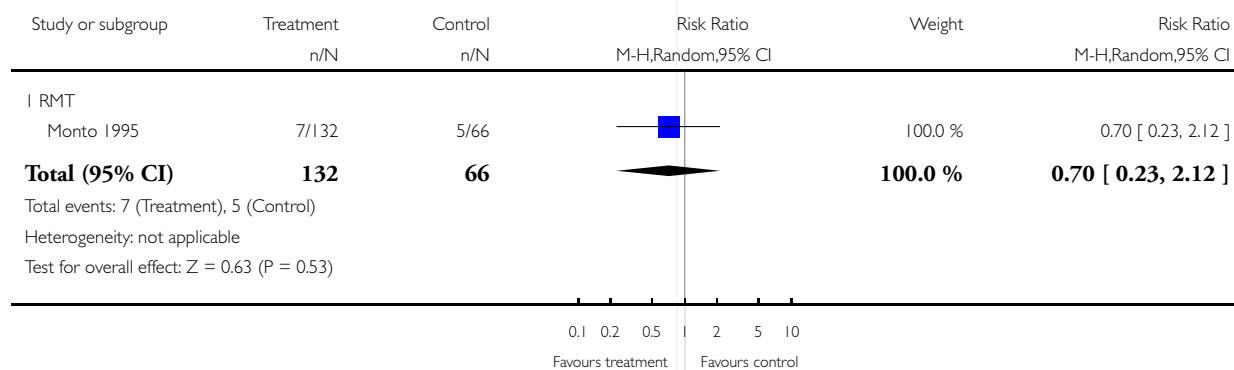


Analysis 5.13. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 13 Dry mouth.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 13 Dry mouth

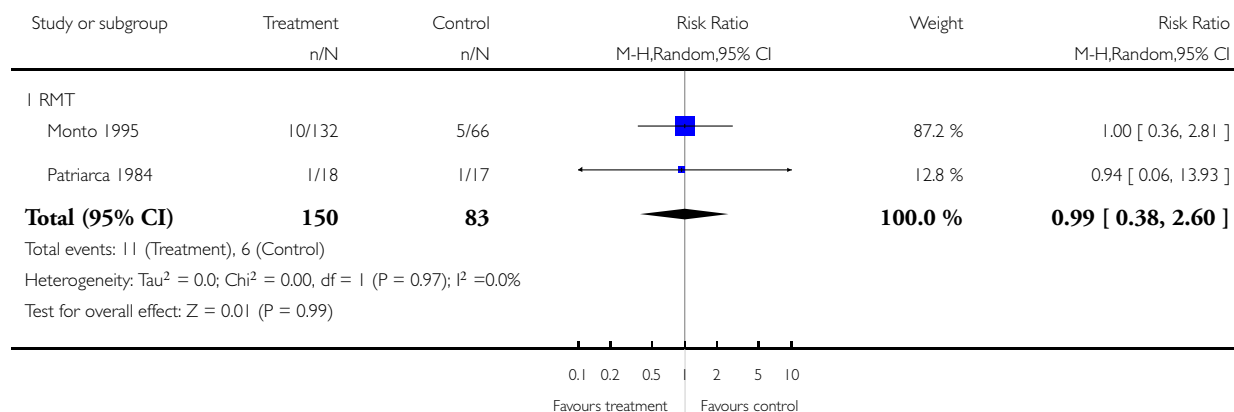


Analysis 5.14. Comparison 5 Adverse effects of AMT and RMT compared to control in the elderly, Outcome 14 Vomiting.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 5 Adverse effects of AMT and RMT compared to control in the elderly

Outcome: 14 Vomiting

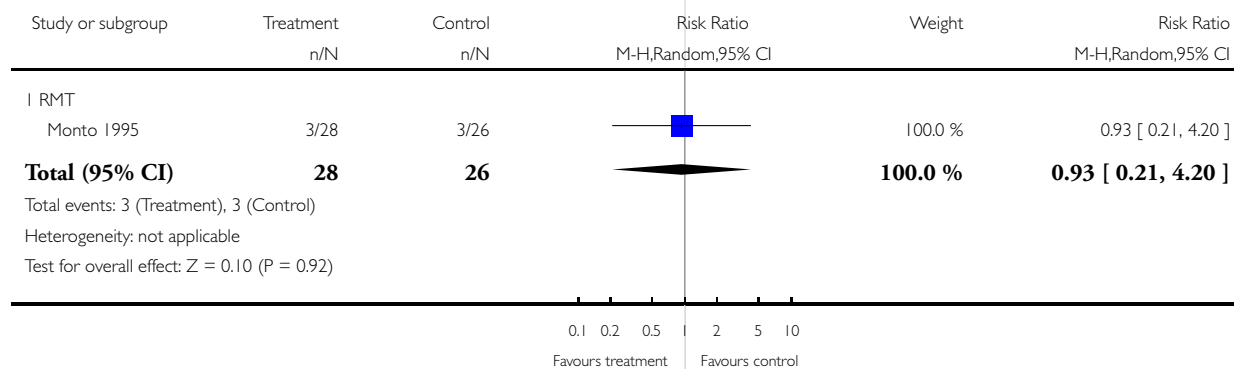


Analysis 6.1. Comparison 6 Use of different doses of AMT and RMT for prophylaxis and treatment of influenza A in the elderly, Outcome 1 Clinical and laboratorial infection.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 6 Use of different doses of AMT and RMT for prophylaxis and treatment of influenza A in the elderly

Outcome: 1 Clinical and laboratorial infection

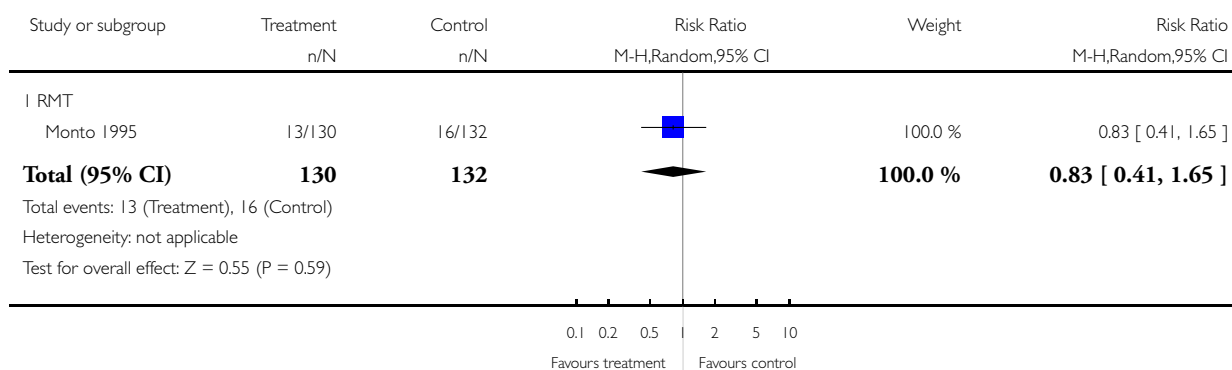


Analysis 7.1. Comparison 7 Adverse effects related to different doses of AMT and RMT in the elderly, Outcome 1 Confusion.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 7 Adverse effects related to different doses of AMT and RMT in the elderly

Outcome: 1 Confusion

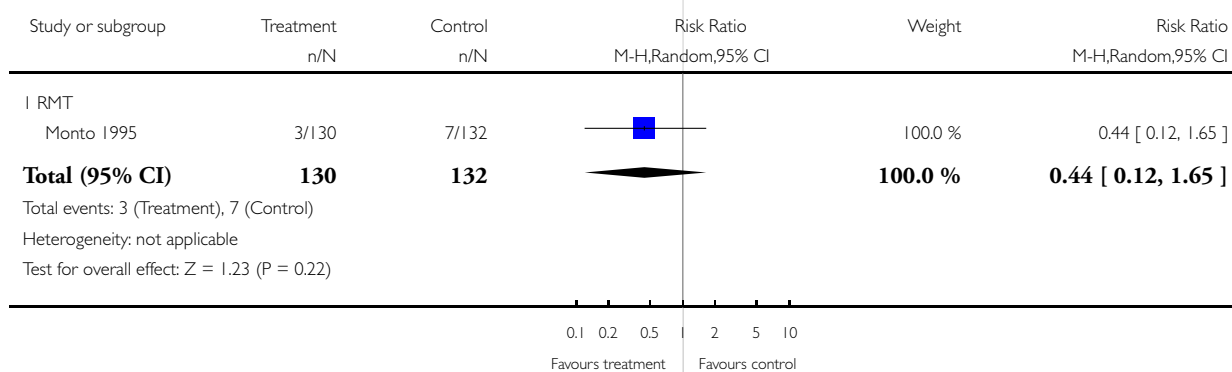


Analysis 7.2. Comparison 7 Adverse effects related to different doses of AMT and RMT in the elderly, Outcome 2 Depression.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 7 Adverse effects related to different doses of AMT and RMT in the elderly

Outcome: 2 Depression

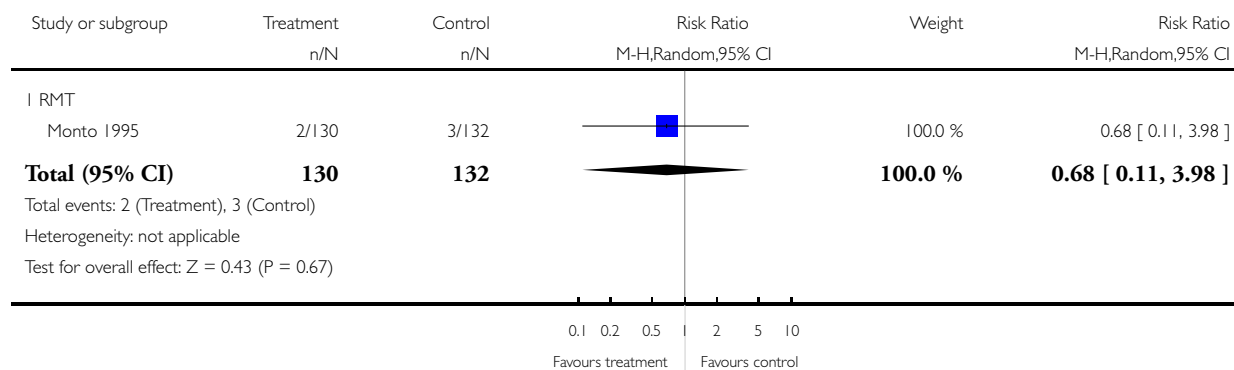


Analysis 7.3. Comparison 7 Adverse effects related to different doses of AMT and RMT in the elderly, Outcome 3 Impaired concentration.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 7 Adverse effects related to different doses of AMT and RMT in the elderly

Outcome: 3 Impaired concentration

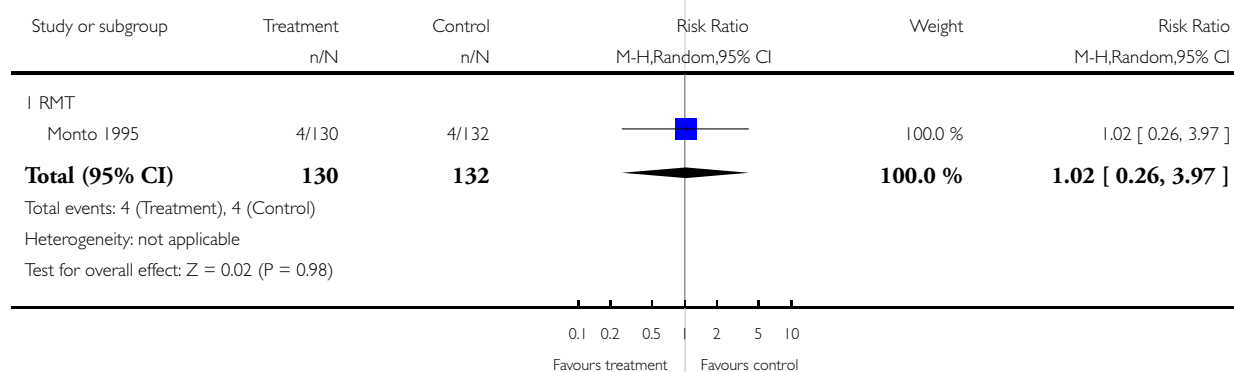


Analysis 7.4. Comparison 7 Adverse effects related to different doses of AMT and RMT in the elderly, Outcome 4 Insomnia or sleeplessness.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 7 Adverse effects related to different doses of AMT and RMT in the elderly

Outcome: 4 Insomnia or sleeplessness

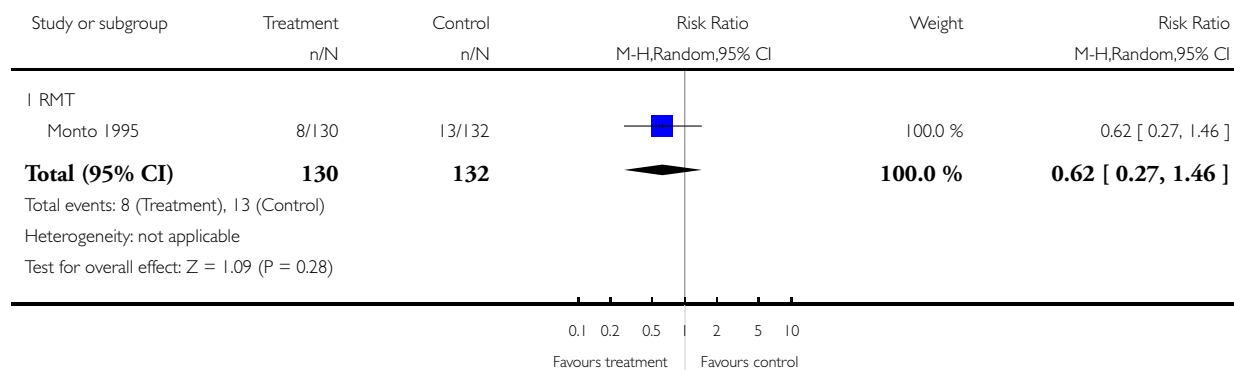


Analysis 7.5. Comparison 7 Adverse effects related to different doses of AMT and RMT in the elderly, Outcome 5 Loss of appetite.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 7 Adverse effects related to different doses of AMT and RMT in the elderly

Outcome: 5 Loss of appetite

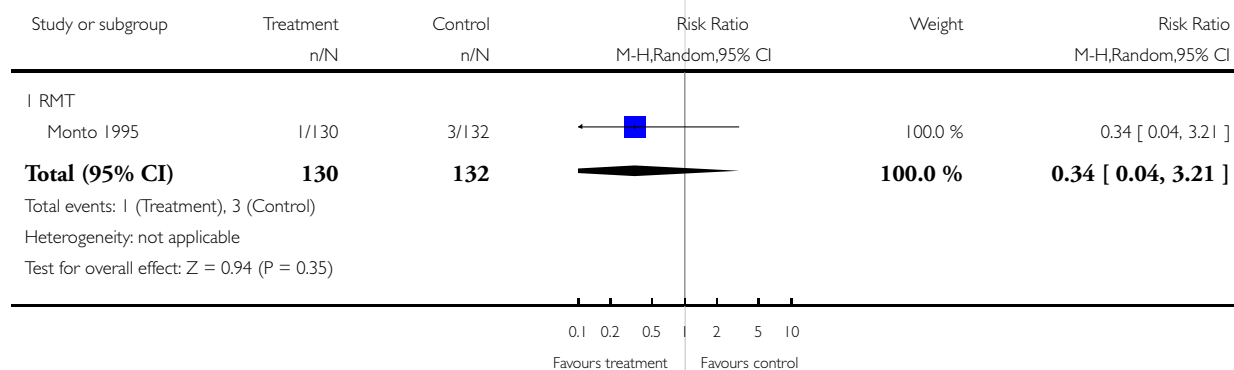


Analysis 7.6. Comparison 7 Adverse effects related to different doses of AMT and RMT in the elderly, Outcome 6 Rash or allergic reaction.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 7 Adverse effects related to different doses of AMT and RMT in the elderly

Outcome: 6 Rash or allergic reaction

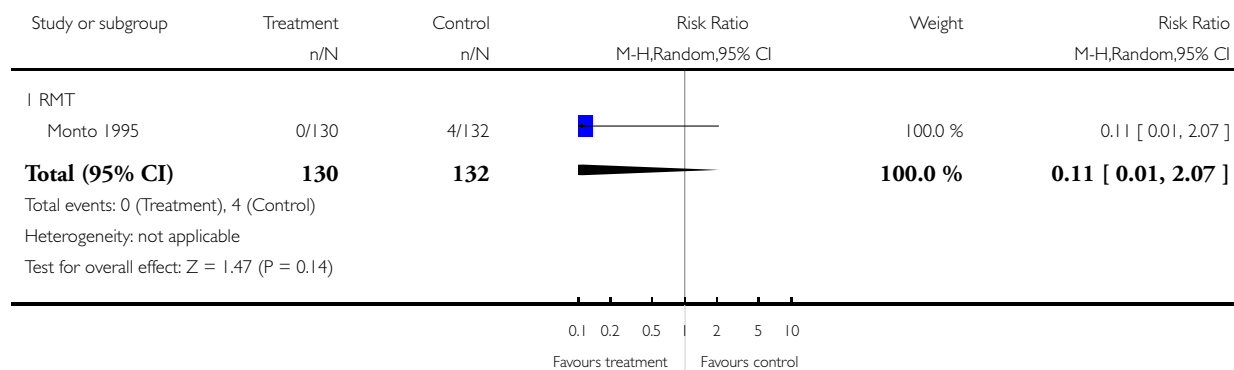


Analysis 7.7. Comparison 7 Adverse effects related to different doses of AMT and RMT in the elderly, Outcome 7 Seizure or clonic twitching.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 7 Adverse effects related to different doses of AMT and RMT in the elderly

Outcome: 7 Seizure or clonic twitching

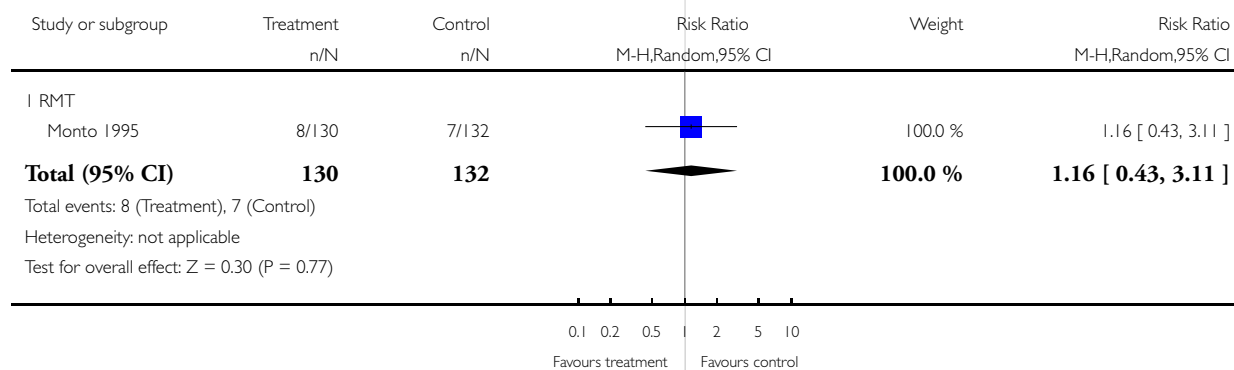


Analysis 7.8. Comparison 7 Adverse effects related to different doses of AMT and RMT in the elderly, Outcome 8 Dry mouth.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 7 Adverse effects related to different doses of AMT and RMT in the elderly

Outcome: 8 Dry mouth

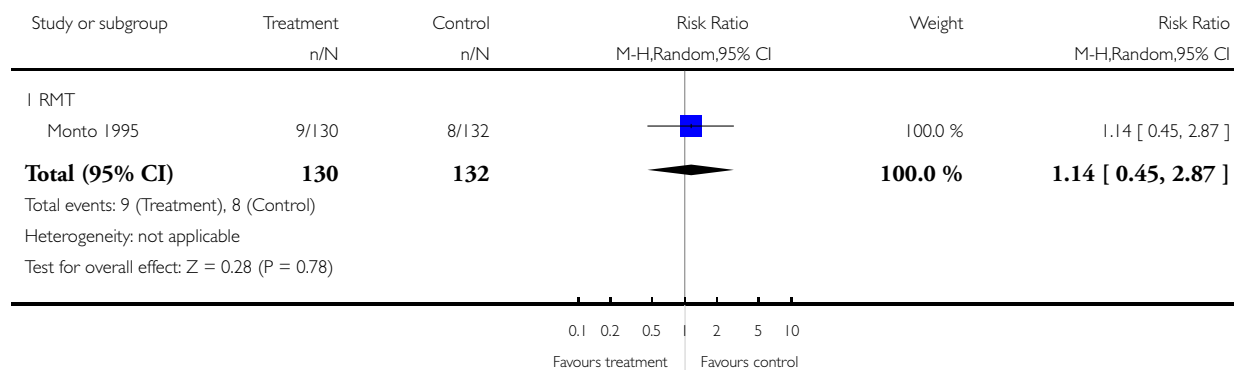


Analysis 7.9. Comparison 7 Adverse effects related to different doses of AMT and RMT in the elderly, Outcome 9 Fatigue and drowsiness.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 7 Adverse effects related to different doses of AMT and RMT in the elderly

Outcome: 9 Fatigue and drowsiness

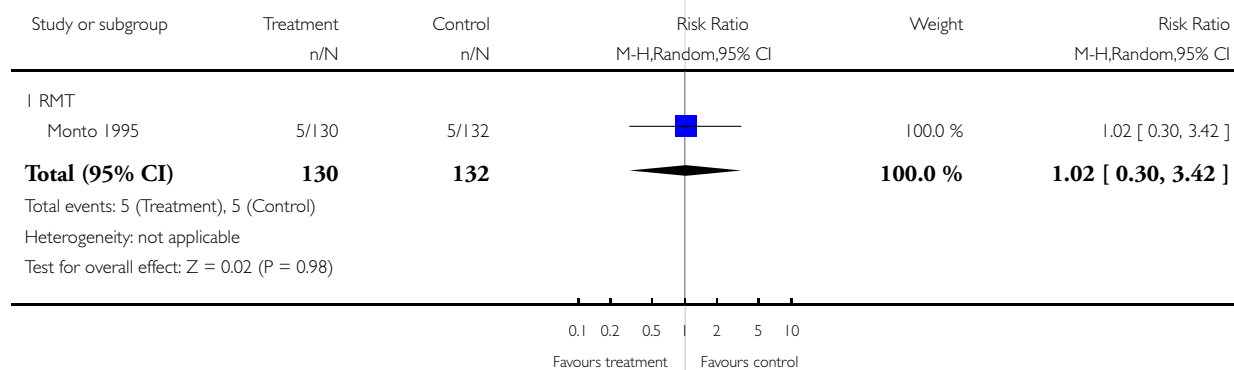


Analysis 7.10. Comparison 7 Adverse effects related to different doses of AMT and RMT in the elderly, Outcome 10 Headache.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 7 Adverse effects related to different doses of AMT and RMT in the elderly

Outcome: 10 Headache

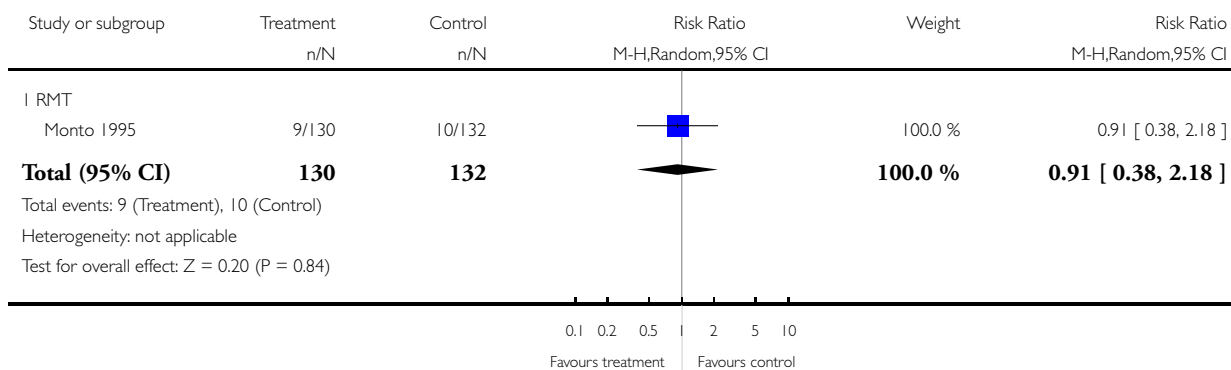


Analysis 7.11. Comparison 7 Adverse effects related to different doses of AMT and RMT in the elderly, Outcome 11 Body weakness or debility.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 7 Adverse effects related to different doses of AMT and RMT in the elderly

Outcome: 11 Body weakness or debility

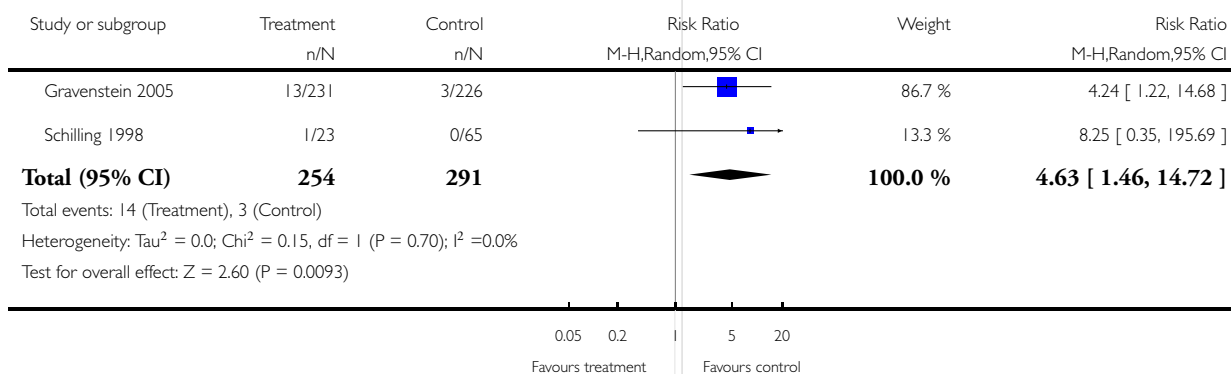


Analysis 8.1. Comparison 8 AMT and RMT compared to other antivirals in the elderly, Outcome 1 RMT and zanamivir.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 8 AMT and RMT compared to other antivirals in the elderly

Outcome: 1 RMT and zanamivir

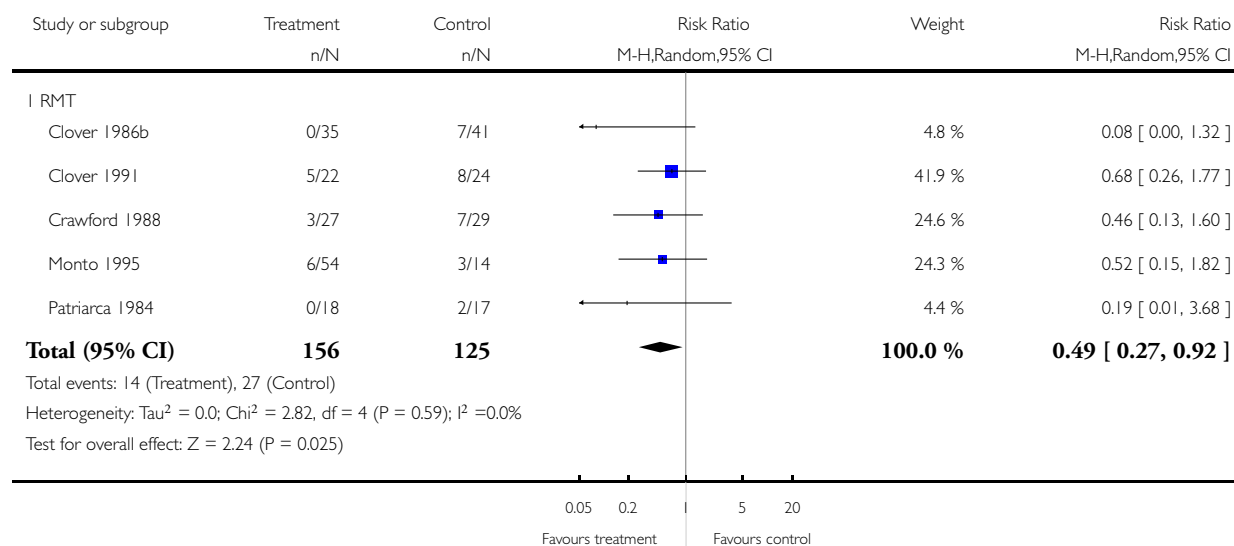


Analysis 9.1. Comparison 9 Additional comparison: RMT compared to control in the prophylaxis of influenza A in children and the elderly, Outcome 1 Infection.

Review: Amantadine and rimantadine for influenza A in children and the elderly

Comparison: 9 Additional comparison: RMT compared to control in the prophylaxis of influenza A in children and the elderly

Outcome: 1 Infection



APPENDICES

Appendix I. EMBASE search strategy

EMBASE (Embase.com)

- 1 exp INFLUENZA/
- 2 influenza.ti. or influenza.ab.
- 3 or/1-2
- 4 exp AMANTADINE/
- 5 amantadine.ti. or amantadine.ab.
- 6 exp RIMANTADINE/
- 7 rimantadine.ti. or rimantadine.ab.
- 8 or/4-7
- 9 3 and 8
- 10 Randomized Controlled Trial/
- 11 Controlled Study/
- 12 exp RANDOMIZATION/
- 13 Single Blind Procedure/
- 14 Double Blind Procedure/
- 15 Crossover Procedure/
- 16 Phase 3 Clinical Trial/
- 17 Phase 4 Clinical Trial/
- 18 or/10-17

FEEDBACK

Amantadine and rimantadine for influenza A in children and the elderly, 24 January 2008

Summary

A year ago CDC provided a recommendation not to use these drugs for 'flu supporting this recommendation by newly acquired resistance of the virus. I believe that this recommendation ought to be at least discussed in the review and better, addressed e.g. by analysis of RCTs data for time periods e.g. before 2000 and after etc.

Also it would be nice to have the abstract rich with data, not just a statement.

Submitter agrees with default conflict of interest statement:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

We do agree that the issue of viral resistance is of utmost importance. We have stressed this concern in the Background and in the Discussion sections. We expect, from what is written in the text, that readers would be aware of the problem.

Background: ...Both drug classes have shown partial effectiveness for prevention and treatment of influenza A viruses, although neuraminidase inhibitors are less likely to promote the development of drug-resistant influenza (Moscona 2005).

Discussion: Data on comparison to other antivirals was available just for RMT and zanamivir for prophylaxis of influenza A in the elderly group. This fact allowed a comparison of drugs of the two different classes of antivirals: M2 ion channel inhibitors and neuraminidase inhibitors. Zanamivir more effectively prevented influenza A in the elderly group (Gravenstein 2005; Schilling 1998). Although the M2 ion channel inhibitors are increasingly subject to viral resistance (Goodman 2006) it does not mean that we should abandon AMT and RMT. These antivirals proved effective for prophylaxis against influenza illness in the 1968 pandemic of "Hong Kong Influenza" and in 1977 pandemic-like event involving "Russian influenza". Although the same resistance marker (Ser31Asn) was present in two isolates of influenza A (H5N1) obtained from patients in China in 2003 and in one lineage of avian and human H5N1 viruses in Thailand, Vietnam, and Cambodia, most tested isolates from a second lineage that has been circulating in Indonesia, China, Mongolia, Russia, and Turkey appear to be sensitive to amantadine (Hayden 2005). Furthermore, the next pandemic virus may be one that, like H2N2, is susceptible to this class of drugs. If the circulating strain were known to be susceptible to M2 inhibitors, these drugs would offer a less costly alternative to other antivirals (neuraminidase inhibitors) for prophylaxis against illness.

Contributors

Vasily Vlassov

Feedback comment added 12 June 2008

WHAT'S NEW

Last assessed as up-to-date: 3 November 2007.

13 May 2009	Amended	No changes - republished to fix technical problem.
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HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 1, 2008

12 June 2008	Feedback has been incorporated	Feedback comment added.
25 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Márcia G Alves Galvão (MG) selected the trials, extracted data and was responsible of the methodological aspects of the review.

Marilene Augusta Rocha Crispino Santos (MS) selected the trials, extracted data, was responsible of the methodological aspects of the review and supervised the day-to-day work of the review.

Antonio Ledo Alves da Cunha (AC) was appointed as an arbitrator to solve disagreements between MG and MS on the selection of the trials. He supervised the work in all phases and provided his experience on the development of the review.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Originally in the protocol we planned to study the drug effect on reduction of fever and cough as they are considered the best predictors on influenza diagnosis. After collecting data, we verified that specific timelines for reduction of signs and symptoms were not reported in the included trials. So, we considered the available data and arbitrarily chose a day of antiviral use to evaluate the response to the treatment. This choice was based on Eccle's study in which clinical manifestations were classified in early and later symptoms (Eccle 2005).

We applied wider age ranges for children than the definition stated in the protocol (participants up to 16 years of age). Trials in older participants who were adolescents by WHO definition (WHO 2007) were also included. Data regarding the proportion of the subgroup which strictly fulfilled the age criterion in protocol were not available in five studies or by contacting the trial authors. The respective age ranges were 1 to 17 years (Clover 1991), 13 to 19 years (Payler 1984), 1 to 18 years (Clover 1986b; Crawford 1988), and 8 to 19 years of age (Finklea 1967).

We planned only to make 12 comparisons. However, whilst analysing data we considered doing an additional comparison and put the two age groups together. As the small samples studied in RMT trials for prophylaxis might have influenced the observed results, we tried to overcome this limitation by combining the trials with RMT in children and in the elderly. It must be stressed that extraneous characteristics between those groups, other than age or previous immunisations, may have occurred, impairing generalisation of these results.

INDEX TERMS

Medical Subject Headings (MeSH)

Amantadine [adverse effects; *therapeutic use]; Antiviral Agents [adverse effects; *therapeutic use]; Influenza, Human [*prevention & control]; Influenza A virus; Randomized Controlled Trials as Topic; Rimantadine [adverse effects; *therapeutic use]; Sex Factors

MeSH check words

Aged; Child; Humans