# Intramuscular penicillin is more effective than oral penicillin in secondary prevention of rheumatic fever — a systematic review

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*Background.* People with a history of rheumatic fever (RF) are at high risk of recurrent attacks and of developing rheumatic heart disease following a streptococcal throat infection. Giving penicillin to these people can prevent recurrent attacks of RF and subsequent rheumatic heart disease. However, there is no agreement on the most effective method of giving penicillin.

*Objectives.* To assess the effects of different penicillin regimens and formulations for preventing streptococcal infection and RF recurrence.

*Search strategy*. We searched the Controlled Trials Register (Cochrane Library Issue 2, 2001), Medline (January 1966 - July 2000), Embase (January 1985 - July 2000), reference lists of articles, and contacted experts in the field.

*Selection criteria*. Randomised and quasi-randomised studies comparing: (*i*) oral with intramuscular penicillin; and (*ii*) 2- or 3-weekly with 4-weekly intramuscular penicillin in patients with previous RF.

*Data collection and analysis*. Two reviewers independently assessed trial quality and extracted data.

*Main results.* Six studies were included (1 707 patients). Data were not pooled because of clinical and methodological heterogeneity of the trials. Four trials (1 098 patients) compared intramuscular with oral penicillin and all showed that intramuscular penicillin was more effective in reducing RF recurrence and streptococcal throat infections than oral penicillin. One trial (360 patients) compared 2-weekly with 4-weekly intramuscular penicillin. Penicillin given every 2 weeks was better at reducing RF recurrence (relative risk (RR) 0.52, 95% confidence interval (CI): 0.33 - 0.83) and streptococcal throat infections (RR 0.60, 95% CI: 0.42 - 0.85). One trial (249 patients) showed that 3-weekly intramuscular penicillin injections reduced streptococcal throat infections (RR 0.67, 95% CI: 0.48 - 0.92) compared with 4-weekly intramuscular penicillin.

*Conclusions.* Intramuscular penicillin seemed to be more effective than oral penicillin in preventing RF recurrence and streptococcal throat infections. Two-weekly or 3-weekly injections appeared to be more effective than 4-weekly injections. However, the evidence is based on poor-quality trials and the use of outdated formulations of oral penicillin.

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Rheumatic fever (RF) is the most important cause of acquired heart disease in children and young adults worldwide.[1] The prevalence of RF and rheumatic heart disease is high in areas with poor socio-economic conditions, overcrowding and limited access to medical care.[2] The option of valve replacement is not available in most instances. As a result RF and rheumatic heart disease cause serious disability, premature death and significant health care expenditure in developing countries. The reduction in prevalence of RF in developed countries preceded the introduction of antibiotics and is probably related to the improvement in these non-medical factors. The severity and prognosis of rheumatic heart disease depend on the extent of the carditis and the frequency of recurrent attacks.

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Prevention of RF may be considered to be prevention of the initial attack (primary prevention) or prevention of recurrent attacks (secondary prevention). The subject of primary prevention of RF and treatment of streptococcal sore throat has been reviewed recently.[3] Secondary prevention is particularly important since even an asymptomatic or optimally treated group A streptococcal (GAS) throat infection can still trigger RF recurrence. The options for secondary prevention are the use of a vaccine against GAS and antibiotic chemoprophylaxis. Unfortunately, the availability of a vaccine is still several years away and antibiotic chemoprophylaxis is the only option available at the moment. There are data to suggest that continuous regular antibiotic prophylaxis can prevent or significantly reduce the development of valvular damage and the prevalence of rheumatic heart disease, with disappearance of pre-existing heart murmurs and reduction in mortality.[4,5] The importance of secondary prevention is well appreciated and several programmes have been established in developing countries.[6]

Penicillin is the drug of choice for the secondary prevention of RF.[7] However, there is uncertainty and controversy regarding the most effective regimen for secondary prevention of RF. Some authorities consider intramuscular injections of benzathine penicillin to be more effective than tablets taken every day.[7-9] However, due to the perceived higher risk of anaphylaxis and the dangers associated with the re-use of needles still practised in some poor communities and the discomfort of intramuscular injections, there is resistance to the use of intramuscular penicillin. The safety issues regarding the use of penicillin injections have resulted in government orders prohibiting penicillin injections in hospitals and clinics.[10]

The aim of this systematic review was to summarise the evidence for the use of penicillin for the secondary prevention of RF and to identify the most effective regimen. This information will be of help to policy makers, health practitioners and researchers in this area.

## Methods

### Objectives

To examine the effects of the different penicillin regimens and formulations for preventing streptococcal infection and RF recurrence.

### Inclusion criteria

Randomised controlled trials of at least 6 months' duration were assessed for inclusion.

Children and adults with a history of RF with or without current evidence of rheumatic heart disease, with the initial diagnosis of RF based on the Jones criteria,[11] modified Jones criteria,[12] and revised Jones criteria,[13] were eligible for the study.

Types of interventions were as follows: (*i*) daily oral penicillin versus intramuscular penicillin; and (*ii*) 2-weekly or 3-weekly versus 4-weekly intramuscular penicillin.

The primary outcomes were RF recurrence, mortality related to RF and rheumatic heart disease, and development of chronic rheumatic heart disease. The secondary outcomes were streptococcal throat infections, compliance and adverse events.

### Search strategy

Using the Cochrane Heart Group strategy, we searched the Controlled Trials Register (Cochrane Library Issue 2, 2001), Medline (January 1966 - July 2000), Embase (1985 - July 2000) and reference lists of articles. We contacted experts in the field for unpublished or ongoing studies.

One hundred and fifty-nine citations were retrieved from the databases and two reviewers independently assessed their titles and abstracts for possible inclusion. Studies fulfilling inclusion criteria were appraised independently by the two reviewers, who abstracted study characteristics and outcome measures onto a pre-designed form. The aspects used to assess the quality of included studies were the method of randomisation, adequacy of concealment of treatment allocation and the rate of completion of follow-up.

### Data analysis

For each study the outcomes were summarised into relative risks (RRs) and 95% confidence intervals (CIs). The chi-squared heterogeneity test as well as visual inspection of the graphs were used to test for homogeneity between the studies and a significance level of less than 0.10 was interpreted as evidence for heterogeneity.

## Results

One hundred and fifty-nine potentially relevant citations were retrieved through the search strategy and 136 of these were excluded on the basis of title and abstract (Fig. 1). Twenty-three papers were retrieved for more detailed evaluation. Fourteen of these were excluded for the following reasons: not trials (5), editorial on primary prevention (1), retrospective study (1), trials comparing penicillin with another antibiotic (2), pharmacokinetic outcomes (1), use of historical controls (2), and follow-up period less than 6 months (2).

### Included studies

Six studies were included in this review. We grouped the studies into those comparing oral with intramuscular penicillin (4 randomised trials, 1 098 patients), 2-weekly with 4-weekly penicillin injections (1 randomised trial, 360 patients) and 3-weekly with 4-weekly intramuscular penicillin injections (1 randomised trial, 249 patients). The trial durations ranged from 1 to 12 years. There was no statistical heterogeneity between the studies. However, the results were not pooled because of differences in trial methodologies and patient characteristics across studies.

### Participants

The ages of the participants ranged from 3 to 24 years. Manifestations of RF in the previous attack were not uniform, some having presented with carditis but with no residual rheumatic heart disease, some having presented with arthritis, and a few with chorea. Patients were followed up every month or every 2 months at which time they were assessed for clinical, bacteriological and serological markers of RF recurrence and streptococcal throat infection.

### Outcome measures

The diagnosis of RF was based on the modified Jones criteria in the four earlier studies[14-17] and the revised Jones criteria for the latest studies.[18,19] Streptococcal throat infections were reported as clinical infection, positive throat culture or raised serological

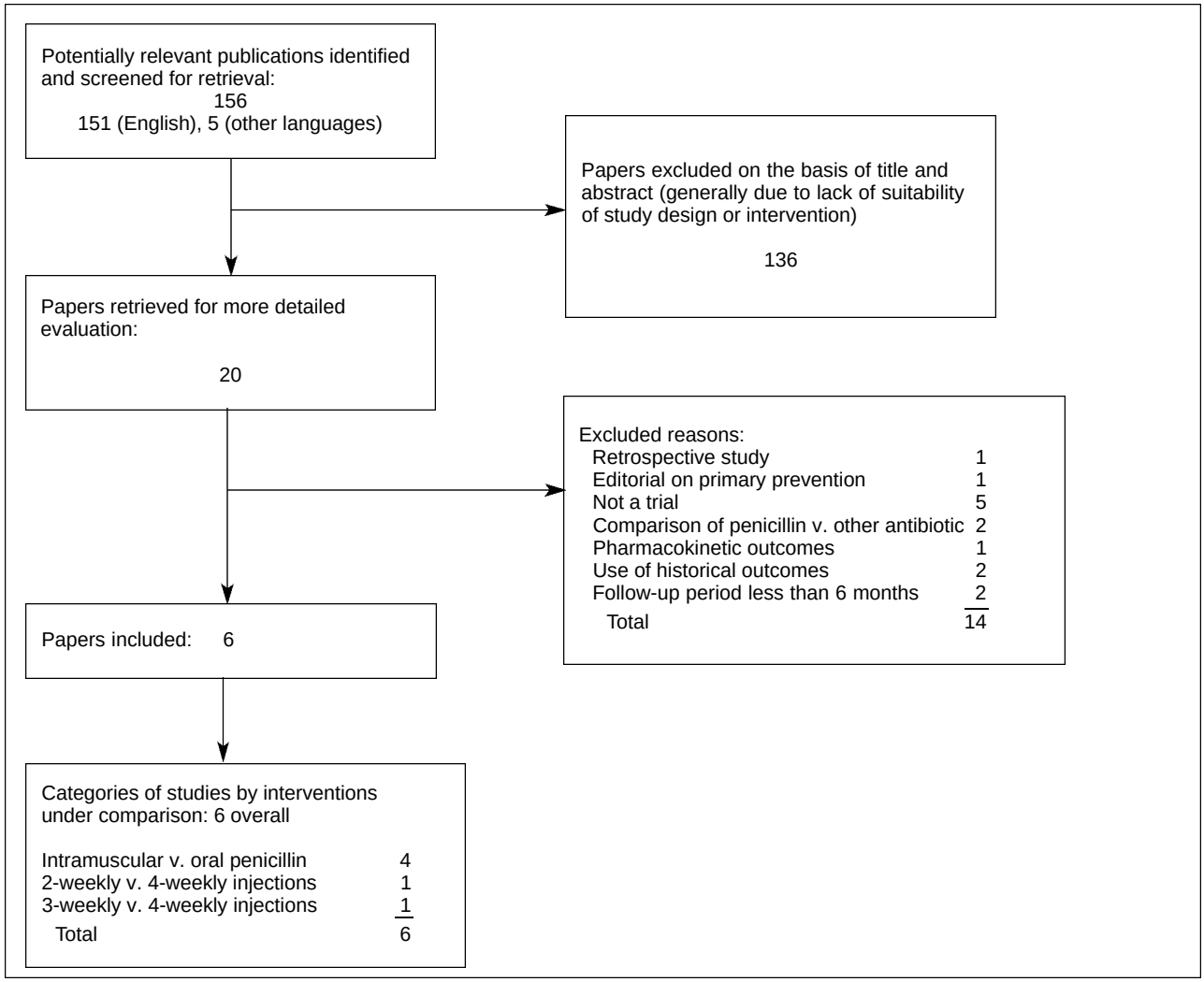


*Fig. 1. The quorum statement.*

markers. The serological test done initially was antistreptolysin O titre (ASOT). In cases where throat culture and ASOT were positive, serial ASOT, hyaluronidase and antistreptokinase were taken. One or all of the following means were used to assess compliance: interview, tablet counts, or average number of injections missed. However, although 6 of the studies assessed compliance, only 2 reported this outcome.[15,18]

### Intramuscular versus oral penicillin (Figs 2 and 3)

One thousand and ninety-eight patients were included in the 4 studies, 561 receiving intramuscular penicillin and 537 receiving oral penicillin. There were 7 RF recurrences among patients receiving intramuscular penicillin and 89 among patients receiving oral penicillin. All 4 studies showed a reduction in the risk of RF recurrence in patients receiving intramuscular penicillin compared with those receiving oral penicillin (Feinstein *et al.*[14] 1959: RR 0.06, 95% CI: 0.01 - 0.48; Wood *et al.*[15] 1964: RR 0.07, 95% CI: 0.02 - 0.27; Feinstein[16] 1965; RR 0.04, 95% CI: 0.01 - 0.30; Feinstein *et al.*[17] 1968: RR 0.13, 95% CI 0.04 - 0.41). There were 78 streptococcal throat infections among patients receiving intramuscular penicillin and 313 among those receiving oral penicillin. Three studies showed significant reduction in streptococcal infection in the intramuscular regimen compared with the oral regimen (Wood *et al.*[15] 1964: RR 0.23, 95% CI: 0.16 - 0.34; Feinstein[16] 1965: RR 0.09, 95% CI: 0.05 - 0.17; Feinstein *et al.*[17] 1968: RR 0.29, 95% CI: 0.21 - 0.40).

### Two-weekly versus 4-weekly intramuscular penicillin (Figs 4 and 5)

Three hundred and sixty patients were included in 1 study, 190 receiving 2-weekly injections and 170 receiving 4-weekly

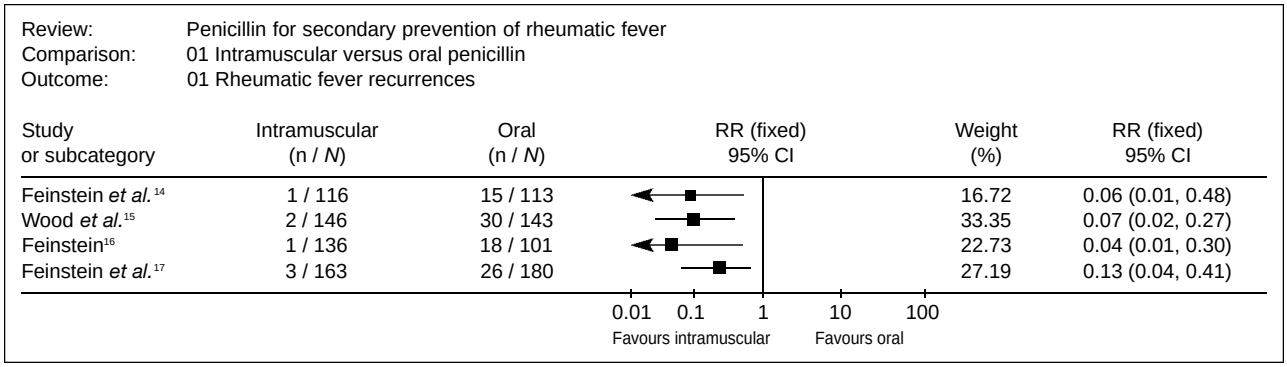


*Fig. 2. Relative risk (95%) of rheumatic fever recurrence for individuals treated with intramuscular or oral penicillin (CI = confidence interval; N = total number in group; n = number with outcome).*

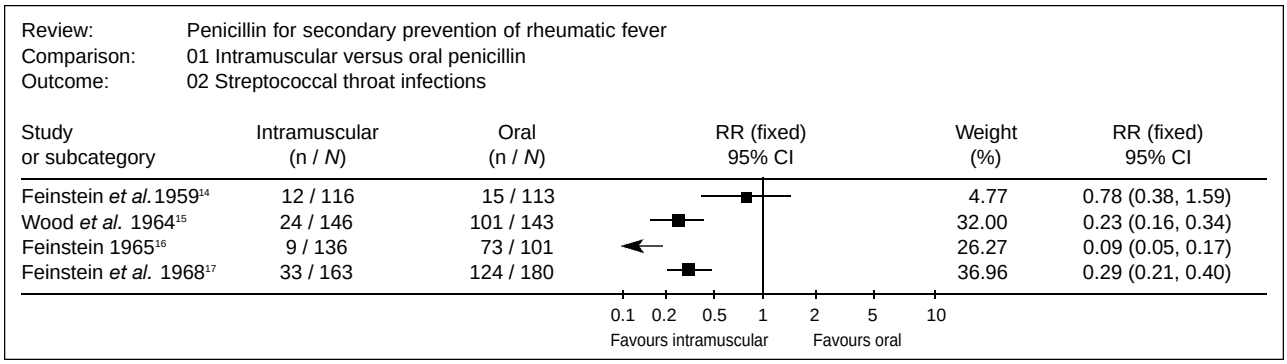


*Fig. 3. Relative risk (95%) of streptococcal throat infection for individuals treated with intramuscular or oral penicillin (CI = confidence interval; N = total number in group; n = number with outcome).*

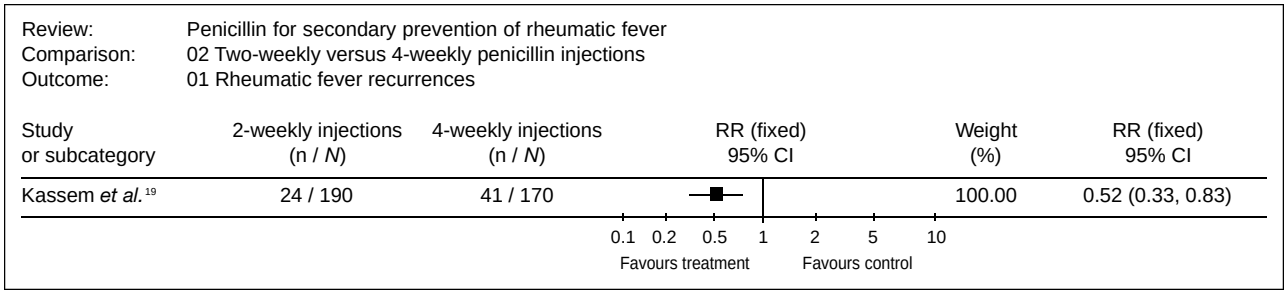


*Fig. 4. Relative risk (95% CI) of rheumatic fever recurrence for individuals treated with 2-weekly or 4-weekly penicillin injections (CI = confidence interval; N = total number in group; n = number with outcome).*

injections.[19] There were 24 RF recurrences among patients receiving 2-weekly injections and 41 among those receiving 4-weekly injections (RR 0.52, 95% CI: 0.33 - 0.83). There were 38 streptococcal infections in the 2-weekly treated group and 57 in the 4-weekly treated group (RR 0.60, 95% CI: 0.42 - 0.85).

### Three-weekly versus 4-weekly intramuscular penicillin (Figs 6 and 7)

This comparison was made in 1 study with 249 patients, 124 receiving 3-weekly injections and 125 receiving 4-weekly injections.[18] There were 9 RF recurrences in the 3-weekly treated group and 16 in the 4-weekly treated group but this difference did not reach statistical significance (RR 0.57, 95% CI: 0.26 - 1.23). There were 39 streptococcal throat infections among children receiving 3-weekly injections and 59 among those receiving 4-weekly injections (RR 0.67, 95% CI: 0.48 - 0.92). This study also reported patient compliance with 3-weekly and 4-weekly injection programmes to be comparable.

### Other outcomes

None of the studies reported on mortality. Adverse events were not presented uniformly in the studies. Wood *et al.*[15] provide 8-

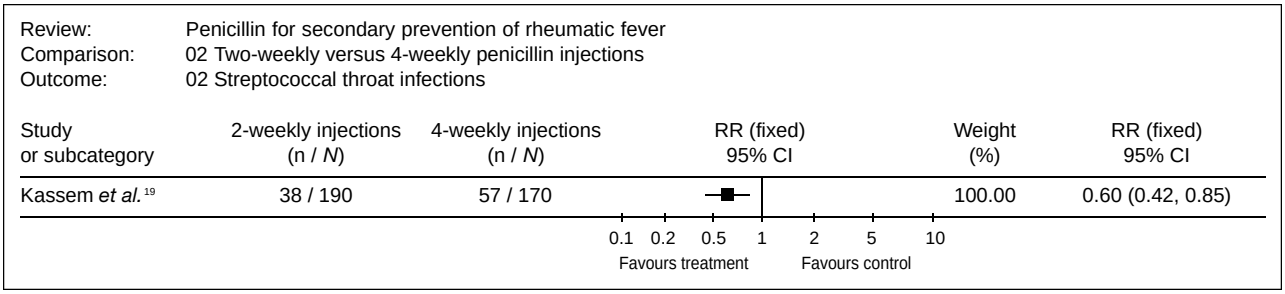


*Fig. 5. Relative risk (95% CI) of streptococcal throat infection for individuals treated with 2-weekly or 4-weekly penicillin injections (CI = confidence interval;* N *= total number in group; n = number with outcome).*

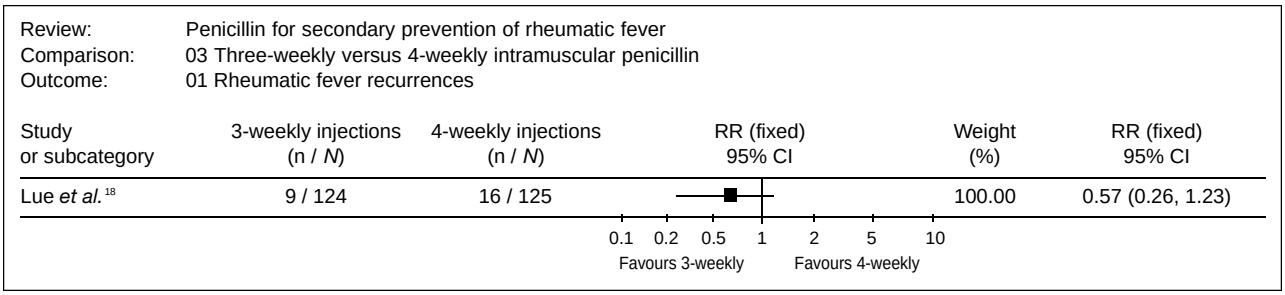


*Fig. 6. Relative risk (95% CI) of rheumatic fever recurrence for individuals treated with 3-weekly or 4-weekly penicillin injections (CI = confidence interval;* N *= total number in group; n = number with outcome).*

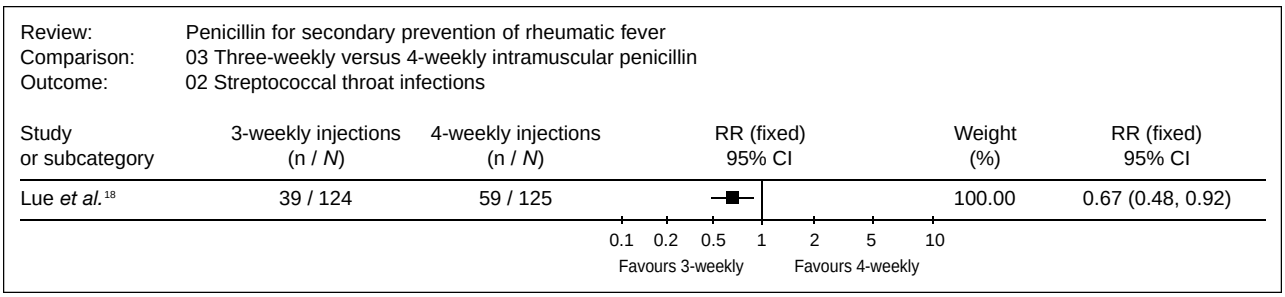


*Fig. 7. Relative risk (95% CI) of streptococcal infection for individuals treated with 3-weekly or 4-weekly penicillin injections (CI = confidence interval;* N *= total number in group; n = number with outcome).*

year follow-up data on cardiac sequelae and mortality for the entire group but the data are not presented separately for each intervention group.

## Discussion

### Main findings

There are two principal findings of this review. First, the evidence seems to be very strong for intramuscular versus oral penicillin, with all 4 studies showing an 87 - 96% reduction in RF recurrence[14-17] and a 71 - 91% reduction in streptococcal throat infection.[15-17] Second, the evidence from this review suggests that more frequent injections are more effective in preventing RF recurrence than 4-weekly injections. This evidence is strong for 2-weekly injections with an almost 50% reduction in the risk of RF recurrence and a 40% reduction in streptococcal throat infections compared with 4-weekly injections.[19] The evidence for 3-weekly injections is less strong and may be even weaker if we take into account the systematic error introduced by inadequate randomisation and allocation concealment in the study.[18]

### Quality of included studies

Treatment allocation was not adequately described in 3 studies[14,16,17] and was not described at all in 1 study.[19] The paper by Lue *et al.*[18] summarises results of a 12-year prospective follow-up study which is reported as 3 separate publications.[18,20,21] Allocation to intervention group was initially based on odd or

even hospital numbers but children recruited between 1985 and 1991 were allocated on the basis of random permutations. It was not possible to sort out results by method of treatment allocation. Of the 343 patients in the later study by Feinstein *et al.*,[17] 216 were admitted from the previous trial[16] and stayed in the groups to which they had been previously allocated. In the 1965 study by Feinstein,[16] 17 patients initially allocated to intramuscular penicillin were transferred to oral penicillin because they were not willing to continue receiving injections. This would have introduced contamination. The outcomes for these patients were not given separately, so it was not possible to perform intention-to-treat analysis. Blinding is not possible when injections are compared with oral tablets and in all comparisons the authors do not indicate whether outcome assessment was blind. Follow-up completion was not reported consistently in the studies. Of the 267 patients initially randomised in the study by Lue *et al.*,[18] 18 were lost to follow-up and were not accounted for in the final result.

Therefore, although the evidence is strong, it is based on studies that were of poor quality. Bias in treatment allocation would exaggerate the true effect of penicillin injections compared with tablets and of 2- or 3-weekly injections compared with 4-weekly injections. When the results are compared according to methodological quality, there was no consistent pattern of poor-quality studies showing a greater or lesser effect size than better-designed studies.

### Types of interventions

The oral penicillin doses and schedules differed between the studies. In 2 studies penicillin tablets were given every day,[14,17] and in 1 study tablets were given only during the first 10 days of every month.[16] The earlier studies used potassium penicillin G.[14,16,17] Phenoxymethyl penicillin (penicillin V), the oral penicillin preparation used today, is more consistently absorbed and produces high blood levels. There is evidence to suggest that this form of penicillin results in low frequency of RF recurrence comparable with benzathine penicillin.[22] Therefore results drawn from this review may not apply to current oral penicillin preparations. Taking tablets is more convenient for patients. However, it is easier to ensure compliance with medication administered by injection. It is therefore possible that the better results with injections were simply because this route of penicillin administration ensured compliance.

### Generalisability

Studies included in the review were conducted in Africa,[19] Asia,[18] and the USA.[14-17] However, the baseline risks of RF were different depending on the geographical area, time period when studies were conducted and host factors in the populations studied and the inclusion criteria used in each study. These factors may limit the applicability of the results in general.

### Limitations of the review

One limitation of this review is the lack of data on the clinically relevant outcomes, namely disappearance of heart murmurs, resolution of valve lesions, mortality due to heart failure and adverse events. Observational studies suggest that oral penicillin is safer than parenteral penicillin in terms of allergic and anaphylactic reactions.[23] The International Rheumatic Fever Study Group, a prospective cohort study from 11 developing countries, showed a 0.2% incidence of anaphylactic reactions with a fatality rate of 0.05%.[24] When viewed in the light of the evidence in favour of penicillin injections from this review, these data suggest that the long-term benefits of prophylactic penicillin injections outweigh the risks.

### Implications for practice and research

Intramuscular penicillin seemed to be more effective than oral penicillin in preventing RF recurrence and streptococcal throat infections. Two-weekly or 3-weekly injections appeared to be more effective than 4-weekly injections. Even though trials in this review were of poor quality, the evidence is strong and it is reasonable to promote current guidelines based on this evidence until further evidence becomes available. There have been anecdotal reports of sudden deaths following benzathine penicillin injections given to people with no prior history of penicillin allergy. In some communities this has led to public and health care workers preferring oral penicillin. If current guidelines for RF secondary prevention are to be implemented, the safety and quality of penicillin injections needs to be assured. Public health education attempts should focus on increasing awareness among RF patients with regard to the need for regular continuous antibiotic prevention and the options available.

In view of the poor quality of the available evidence, well-designed randomised controlled trials comparing the effectiveness of penicillin injections with oral phenoxymethylpenicillin are required. Such studies should be of long duration to allow for the measurement of clinically important outcomes, namely resolution of heart murmurs, improvement in signs and symptoms of heart failure, reduction in mortality, and cost-effectiveness of the different treatment regimens. Pharmacokinetic studies have demonstrated that penicillin injections given every 2 or 3 weeks ensure penicillin levels above the minimum inhibitory concentration.[25-27] These findings are in support of the 2-weekly or 3-weekly injections. There is still a need for well-designed multi-centre randomised controlled trials to establish whether these surrogate outcomes translate to clinical benefit. Regarding the safety of intramuscular penicillin, there is need to set up surveillance

and adverse drug reaction monitoring systems. Penicillin injections administered with a local anaesthetic cause less discomfort and there is a suggestion that they may be associated with fewer sudden deaths. This question needs to be addressed in future trials. RF patients and their families should be involved in discussions to set research priorities that answer questions relevant to their needs.

Preliminary work on this systematic review was started when one of the authors (JM) was based in the Department of Medicine, University of Zimbabwe, with support from AusAid and the Centre for Clinical Epidemiology and Biostatistics, Newcastle, Australia. It was subsequently updated and completed in the UK with methodological and technical support from the Cochrane Heart Group and a bursary from the Cochrane Health Promotion and Public Health Field.

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