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Overview of Reviews

The Cochrane Library and the Treatment of Sore Throat in Children and Adolescents: An Overview of Reviews

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Background: Sore throat is a common respiratory tract symptom responsible for 6% of children's visits to pediatricians or family physicians. Even though sore throat is usually self-limiting, antibiotics are often prescribed in hopes of decreasing symptom length and the risk of developing sequelae. However, antibiotic over-prescription could lead to adverse events in individuals and bacterial resistance in the community, so the efficacy and safety of antibiotics must first be established, and alternative treatment options should also be investigated.

Objectives: This overview of reviews aims to synthesize evidence from the *Cochrane Database of Systematic Reviews* (CDSR) on the efficacy and safety of different antibiotic treatment strategies (standard antibiotics, delayed antibiotics, short-duration antibiotics and different types of antibiotics) to improve symptoms of sore throat in children and adolescents. The efficacy and safety of two other treatments, steroids and Chinese herbal medicine, are also investigated.

Methods: Issue 1, 2011 of the CDSR was searched for all reviews examining the treatment of sore throat and disorders which commonly have sore throat as part of their clinical presentation. We also searched for reviews examining the prevention of important sequelae of sore throat. All systematic reviews examining pharmacologic or non-pharmacologic treatments in children were identified, and data were extracted, compiled into tables and synthesized using quantitative and qualitative methods.

Main results: Data pertaining to sore throat in children and adolescents were extracted from seven Cochrane reviews. Antibiotics provided only modest benefit over placebo for symptoms of sore throat and fever. Immediate versus delayed prescription of antibiotics resulted in a 58% decrease in severity of pain due to sore throat on day three (RR: 0.42; 95% CI: 0.33, 0.54), and a significant, moderate decrease in fever on day three (SMD: −0.53; 95% CI: −0.74, −0.31). Most studies of macrolides, cephalosporins and carbacephem showed no significant benefit over oral penicillin for resolution of symptoms, but in two trials a short course of a cephalosporin compared to oral penicillin led to modest decreases in both sore throat (half a day; MD: −0.50; 95% CI: −0.78, −0.22) and fever (seven hours; MD: −0.30; 95% CI: −0.45, −0.14). Steroids compared to placebo decreased symptoms of sore throat in children with infectious mononucleosis at 12 hours (RR: 0.54; 95% CI: 0.30, 0.99) but not at any other measured time points. A higher rate of vomiting was associated with delayed antibiotics (RR: 0.07; 95% CI: 0.03, 0.20); vomiting, diarrhea and abdominal pain were associated with short-duration antibiotics (RR: 1.74; 95% CI: 1.31, 2.32); and overall adverse effects were associated with macrolides (RR: 2.19; 95% CI: 1.04, 4.61). Trials involving Chinese herbal medications for sore throat were of low quality and no good evidence for the use of these agents was available.
Antibiotics compared to placebo were associated with lower rates of acute rheumatic fever, but the difference was not statistically significant when only pediatric data were included (RR: 0.20: 95% CI: 0.01, 4.18). One review examining the secondary prevention of rheumatic fever found that intramuscular versus oral penicillin reduced the recurrence of rheumatic fever by 92% (RR: 0.08; 95% CI: 0.04, 0.18) and significantly reduced the number of participants who developed streptococcal throat infections (RR: 0.22; 95% CI: 0.17, 0.27; I^2: 81%).

Authors' Conclusions: Evidence from the CDSR suggests that antibiotics provide only modest improvements in symptoms of sore throat in children and adolescents. If antibiotics are prescribed, macrolides are less ideal

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compared to other agents, and there is some evidence that a short course of a newer cephalosporin may be slightly better than a standard course of penicillin. Any potential benefit of antibiotic treatment must be weighed against the cost of treatment and the possibility of adverse effects. Children with a past history of rheumatic fever or those living in a region with a high prevalence of this condition are more likely to benefit from antibiotics than those without these risk factors. Oral corticosteroids can decrease sore throat symptoms within the first day and may be helpful for children with severe symptoms of infectious mononucleosis. There is no compelling evidence that any Chinese herbal medicine has beneficial effects for the relief of sore throat symptoms or prevention of sequelae.

Editors' Note: *Overviews of reviews, compiling evidence from multiple Cochrane reviews into one accessible and usable document, is a regular feature of this journal. Our aim for each overview is to focus on the treatment question, 'which treatment should I use for this condition?', and to highlight the Cochrane reviews and their results in doing so. It is our hope that the overview will serve as a 'friendly front end' to the Cochrane Library, allowing the reader a quick overview (and an exhaustive list) of Cochrane reviews relevant to the clinical decision at hand.*

Plain Language Summary

Sore throat is a common respiratory symptom that affects 30% of people every year. Sometimes sore throats are treated using antibiotics, but antibiotics will only work if the sore throat is caused by bacteria – they will not work if the sore throat is caused by a virus. Unfortunately, there is no test that can tell for sure whether the sore throat is bacterial or viral, and doctors often hesitate to prescribe antibiotics because they can have side effects like nausea, vomiting, diarrhea, rash and allergic reactions. If your child has a sore throat, it will probably go away in about one week without antibiotics and without other treatments like steroids or herbal medicines. If your doctor does prescribe antibiotics, he or she will probably prescribe ten days of penicillin or three to six days of a newer antibiotic.

Background

Description of the condition

Sore throat is a common respiratory tract symptom which affects up to 30% of people in any given year (1) and is responsible for approximately 6% of children's visits to pediatricians or family physicians (2). Most cases of sore throat are self-limiting, and for 85% of people this resolution occurs within one week (3). Sore throat can be either viral or bacterial, with 50% to 80% of cases being viral. Common causative viral agents include influenza, parainfluenza, infectious mononucleosis (glandular fever), adenoviruses and herpes simplex virus. Sore throat is often a symptom of acute respiratory tract infections such as laryngitis, pharyngitis, tonsillitis and the common cold (3–5). In the past, group A beta-hemolytic streptococcus (GABHS) has been the primary bacterial pathogen of interest (4, 6). More recently, *Fusobacterium necrophorum* has been identified as an uncommon but important bacterial pathogen, affecting up to 10% of adolescents presenting with sore throat and equalling GABHS as a cause of hospitalization for respiratory infection (7).

Unfortunately, signs and symptoms of sore throat do not reliably distinguish children with self-limited viral pharyngitis from those with a bacterial cause, and even complex decision rules that combine specific signs and symptoms frequently misclassify viral cases as bacterial and vice versa (8). Throat culture or rapid antigen testing can aid in determining the cause of the sore throat, but both have relatively high rates of false positives and false negatives. Most clinicians currently have no access to a diagnostic test for *Fusobacterium necrophorum*.

Sore throat caused by GABHS infection can result in sequelae such as acute glomerulonephritis and rheumatic fever, which are of great concern to clinicians. Post-streptococcal glomerulonephritis can occur following a GABHS infection of the throat or skin, and is often self-limiting and treated with supportive measures. Rheumatic fever develops within four weeks of the initial GABHS pharyngitis and is a multisystem inflammatory condition which occurs in 1–3% of children. While often self-limiting, it may induce rheumatic heart disease, which occurs in 1–5% of those who develop rheumatic fever. Rheumatic heart disease is uncommon in industrialized societies but is of great clinical concern in the developing world, causing upwards of 200,000 deaths per year (9). Moreover, the recurrence of rheumatic fever rises to almost 50% in patients with a previous episode of rheumatic fever. Both complications are believed to be preventable by antibiotic treatment following GABHS infection.

Description of the interventions

Since sore throat is usually self-limiting, general management of children with sore throat should include parental reassurance, pain relief and information about the natural progression of the illness (3). While antibiotics are regarded as standard treatment for sore throats

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of suspected bacterial etiology, a variety of additional interventions are also available. This overview examines current evidence for six interventions used in the management of sore throat in children: standard antibiotics, newer antibiotics (i.e. cephalosporins, macrolides and carbacephem), delayed antibiotics, short-duration antibiotics, steroids and Chinese medicinal herbs. These treatments have been studied with the aim of improving symptom control and reducing sequelae and adverse events.

How the interventions might work

For the subset of children with bacterial sore throats, *antibiotics* could decrease the length or severity of the illness and could also decrease recurrence rates. A small proportion of children with sore throat develop otitis media, peritonsillar abscess or cellulitis following their bacterial sore throat. These infections can be severe, may require hospitalization and might be prevented by early administration of antibiotics (10). A small proportion of children with GABHS develop serious and potentially life-threatening sequelae such as rheumatic fever or glomerulonephritis or, for adolescents with *F. necrophorum* infections, Lemierre syndrome (11–14). In the Western world, antibiotics are currently over-prescribed: 53–73% of children presenting with sore throat receive antibiotics, whereas only 15–36% of sore throats are caused by bacterial infections (2, 4, 6). This unnecessary prescribing could result in community bacterial resistance and individual adverse events such as nausea, vomiting, diarrhea, candidiasis, rash and allergic reactions (3, 5, 15).

Delayed prescribing of antibiotics could serve to both decrease antibiotic over-prescription and allow antibiotics to be used for children with bacterial infections by providing time for viral sore throats to resolve without treatment. Delayed antibiotics have been advocated since the late 1990s (4) and involve advice from clinicians to caregivers to fill an antibiotic prescription after two or three days only if symptoms persist or worsen (5). This strategy could improve parent satisfaction with treatment and could also serve as a 'safety net' for the small proportion of patients who develop worsening symptoms due to bacterial infection and subsequently fill their prescriptions (16, 17).

Short-duration instead of standard-duration antibiotics might also circumvent some limitations of standard antibiotic therapy. 'Short-duration antibiotics' refer to newer antibiotics (e.g. azithromycin, clarithromycin and cefuroxime) prescribed for 2–6 days, while 'standard-duration antibiotics' typically refer to 500 mg of penicillin taken two to four times daily for ten days. Patient compliance with standard-duration antibiotics decreases with symptom remission (18), therefore the compressed time frame of short-duration antibiotics might improve medication compliance and decrease adverse effects, treatment failure, return visits, sequelae and the potential for community bacterial resistance (19, 20).

Non-antibiotic treatments for sore throat include steroids and Chinese medicinal herbs. *Steroids* are used to treat inflammatory symptoms of both bacterial and viral sore throats, and these potent anti-inflammatory agents target potential inflammation of the neck glands, pharynx and/or tonsils (21, 22). However, controversy exists around the use of a drug with potential short and long-term adverse events to treat a disorder that is typically self-limiting (23). Chinese medicinal herbs have been used for thousands of years to treat sore throat, and some Chinese herbal preparations have been shown to have antitussive, antipyretic and expectorant effects (15). However, research is still needed to determine whether Chinese herbs can be used to relieve sore throat and, if so, which herbs work best. In addition, Chinese herbs may not be entirely safe, with possible adverse effects including allergic reactions and Chinese herbal nephropathy (24–26).

Why it is important to do this overview

Sore throat is of considerable interest to the medical community due to its prevalence and the large number of associated healthcare consultations. The annual cost in the USA due to GABHS alone has been estimated to be $224 to $539 million (27). Non-medical costs make up almost half of this amount. Children miss an average of 1.8 days of school per sore throat episode, and their parents require an average of 1.9 days off work. Furthermore, sequelae of sore throat infections have significant associated morbidity and mortality, especially in developing nations. Clinicians and parents presented with a child with sore throat face difficult decisions about whether to use antibiotics or other treatments, when to start treatment, how long to continue treatment, and whether to treat at all. An overview of systematic reviews on the treatment of sore throat can inform these decisions by providing estimates of the expected benefits and risks of various treatment strategies.

Objectives

This overview of reviews aims to synthesize the current evidence from the *Cochrane Database of Systematic Reviews* on the efficacy and safety of pharmacologic and non-pharmacologic treatments to improve symptoms of sore throat in children and adolescents.

Methods

Criteria for considering reviews for inclusion

Reviews were included providing they were published in the *Cochrane Database of Systematic Reviews* (CDSR) and examined pharmacologic or non-pharmacologic interventions for the treatment of sore throat in children or adolescents. Because sore throat is a

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Search term		Results
#1	'sore throat' in Cochrane Reviews	97
#2	(strep* throat) in Cochrane Reviews	42
#3	(strep* pharyngitis) in Cochrane Reviews	24
#4	(group A strep* infection) inCochrane Reviews	205
#5	'respiratory tract infection' in Cochrane Reviews	149
#6	MeSH descriptor Pharyngitis explode all trees with qualifiers: CO, DT, DE, DI, PC, TH	559
#7	MeSH descriptor Tonsillitis explode all trees with qualifiers: CO, DT, DE, DI, PC, TH	227
#8	MeSH descriptor Laryngitis explode all trees with qualifiers: CO, DI, DT, PC, TH	98
#9	MeSH descriptor Infectious Mononucleosis explode all trees with qualifiers: CO, DT, DI, PC	42
#10	MeSH descriptor Herpes Simplex explode all trees with qualifiers: CO, DT, DI, PC	652
#11	MeSH descriptor Common Cold explode all trees with qualifiers: CO, DT, DI, PC	304
#12	'influenza' in Cochrane Reviews	121
#13	(measle* OR mump* OR rubella) in Cochrane Reviews	20
#14	'varicella' in Cochrane Reviews	29
#15	MeSH descriptor Glomerulonephritis explode all trees with qualifiers: CO, DT, DI, PC	424
#16	'guttate psoriasis' in Cochrane Reviews	16
#17	MeSH descriptor Rheumatic Fever explodeall trees with qualifiers: CO, DT, DI, PC	86
#18	(#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)	446
#19	throat* in Cochrane Reviews	288
#20	(#18 AND #19)	93
#21	(#1 OR #2 OR #3)	115
#22	(#20 OR #21)	128
#23	(child* OR p?ediatr* OR preschool* OR adolescen* OR youth OR teen* OR infan* OR baby OR babies OR girl* OR boy* OR neonat* OR newborn*) in Cochrane Reviews	3592
#24	(#22 AND #23)	119

Figure 1. Search strategy for Issue 1, 2011 of the *Cochrane Database of Systematic Reviews*

main symptom of many other disorders, reviews were also deemed potentially relevant if they examined treatment of any of the following disorders which typically have sore throat as part of their clinical presentation: acute respiratory tract infections, common cold, glandular fever (infectious mononucleosis), group A streptococcal pharyngitis, herpes simplex, influenza, laryngitis, measles, mumps, pharyngitis, rubella, tonsillitis and varicella. In order to be included in this overview, reviews on the above topics had to include the outcome of 'sore throat'. Reviews examining prevention of three sequelae of sore throat – glomerulonephritis, guttate psoriasis and rheumatic fever – were also deemed potentially relevant and were included if they contained outcome data on occurrence or recurrence of the sequelae. The complete search strategy can be found in Figure 1.

Search methods for identification of reviews

For this overview, Issue 1, 2011 of the CDSR was searched for all reviews examining sore throat, disorders which commonly cause sore throat, and sequelae commonly associated with sore throat. The complete search strategy can be found in Figure 1. We also consulted the Cochrane Acute Respiratory Infections Group to ensure that we did not miss any relevant reviews.

Outcome measures

The following *a priori* outcomes were specified for inclusion in this overview: sore throat, fever, overall symptoms, recovery, recurrence, administrative outcomes, sequelae and adverse effects.

Data collection and analysis

For this overview, one reviewer (MF) extracted the following information from each of the included reviews: inclusion criteria (including populations, interventions, comparisons, and outcomes), methodological quality assessments and numeric results. Random effects modelling was used for all meta-analyses in order to provide the most conservative estimate, and when data were presented in the reviews using fixed effects modelling, Review Manager 5 was used to re-analyse the data using random effects modelling (28). A research assistant subsequently verified the accuracy of all numeric results.

All dichotomous data were summarized using relative risks (RR) with 95% confidence intervals (CI) and were interpreted as statistically significant if the 95% CIs did not cross one. To measure the treatment effect for dichotomous outcomes that reached statistical significance, 'number needed to treat' (NNT) was calculated. For all comparisons, including those based on a single trial, NNT was calculated from the trials' baseline risk (the risk of the event occurring for those not receiving treatment) (29).

Continuous data were summarized using either standardized mean differences (SMD) or mean differences (MD), both with 95% CIs. SMD was calculated for outcomes when a variety of different scales were used across studies, because expressing the effects as

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standardized values allowed results from the different scales to be combined. MD was calculated when the same scale (e.g. 'days') was used to measure the outcomes. Effect sizes expressed using SMD were described as small (<0.40), moderate (0.40–0.70) or large (>0.70) based on decision rules outlined in the *Cochrane Handbook* (29). SMD and MD results were interpreted as statistically significant if the 95% confidence intervals did not cross zero.

If more than one study contributed to the meta-analysis, the accompanying I^2 value was reported and represents the degree of statistical heterogeneity among the studies. An I^2 value close to 0% indicates minimal or no heterogeneity of trials, whereas an I^2 of 50% or greater represents substantial heterogeneity (29). I^2 values of 50% or greater were included in the results text along with the effect size.

Results

Results of the search

The search strategy (see Figure 1) returned 119 reviews, of which 37 were potentially relevant. Four reviews and two protocols examined the treatment of sore throat: the four reviews were included in this overview (15, 30–32) and the two protocols were excluded as they were not yet available in full review format. Twenty-eight reviews or protocols examined the treatment of disorders which commonly have sore throat as part of their presentation; three of these reviews included 'sore throat' as an outcome measure and were therefore included in this overview (23, 33, 34). Lastly, three reviews examined common sequelae of sore throat; one of these reviews included the outcome of 'recurrence' and was therefore included in this overview (35).

Description of included reviews

Eight reviews, containing a total of 43 relevant trials and 18,393 participants, were included in this overview (15, 23, 30–35). Seven of the included reviews examined interventions for the treatment of sore throat, including antibiotics (30, 31, 33), delayed antibiotics (32), short-duration antibiotics (34), steroids (23) and Chinese herbal medicine (15). The eighth review examined secondary prevention of rheumatic fever (35).

All but one of the included reviews were published in 2010, and the exception (35) was published in 2009. The eight included reviews contained a total of 104 trials, but only 43 of those trials (41%) contained child-only data and were included in this overview. The rest were excluded because they enrolled participants of all ages, and child-specific data could not be extracted separately. Seven of the included reviews contained between one (15) and seven (31) pediatric trials, and the number of children included in these reviews ranged from 85 (23) to 1,929 (31). The last review (34) contained 19 pediatric trials and 12,892 children. Table 1 presents the study characteristics of the eight included reviews.

Search methods

All included reviews searched CENTRAL, MEDLINE and EMBASE. Six reviews (15, 23, 30, 33–35) searched for unpublished and/or ongoing trials, five reviews (30–32, 34, 35) hand-searched reference lists of relevant trials, and four reviews (30, 33–35) contacted experts and/or authors. Two reviews each also searched conference proceedings (30, 34), specialized journals (15, 30) and contacted pharmaceutical companies (30, 34).

Participants

The participants included in this overview had heterogeneous clinical diagnoses. One review (31) included participants with 'symptoms of sore throat', and a second review (15) specified that the sore throat had to be due to pharyngitis, laryngitis or tonsillitis. Two reviews (32, 33) included participants with various acute respiratory tract infections, and another two (30, 34) included participants with laboratory confirmed GABHS infections. One review (23) examined participants with infectious mononucleosis; lastly, one review (35) included participants with a history of rheumatic fever.

Ages of participants were fairly similar across reviews. Seven reviews included participants of all ages, and pediatric data was able to be extracted separately. In five of the reviews (15, 23, 30, 31, 35) the ages of children ranged between 6 months and 18 years, and the other two reviews (32, 33) did not specify age ranges of children. The last review (34) included children between 1 and 18 years of age.

Interventions

All interventions included in this overview were pharmacologic, except for one non-pharmacologic intervention examining Chinese herbal medicines (15). Five reviews (15, 30, 32, 34, 35) compared an active treatment to another active treatment, and three reviews (23, 31, 33) compared an active treatment to placebo. Specifically, the included reviews examined the following nine comparisons for the treatment of sore throat:

- Any antibiotic versus placebo for sore throat ('any antibiotic' refers to any type, duration, repetition schedule or mode of administration) (seven trials)
- Any antibiotic versus placebo for common cold/acute purulent rhinitis ('any antibiotic' refers to any type, duration, repetition schedule or mode of administration) (five trials)[1]

[1] One of these trials (36) is also included in the previous comparison because it met the inclusion criteria for both comparisons. The trial has been included in all relevant meta-analyses.

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Table I. Characteristics of included reviews

Review title	Authors	Last assessed as up-to-date	Number of studies (children only)	Study sample size (range)	Population	Inclusion criteria	Intervention	Comparison	Outcomes for which data are reported
Antibiotics for the common cold and acute purulent rhinitis	Arroll B, Kenealy T	August 2009	11 (5)	All studies: 2,656 (33–763) Children only: 780 (89–261)	All ages	Acute URTI with symptoms lasting seven days or less. Pharyngitis, bronchitis and pneumonia were excluded	Any antibiotic	Placebo	Persisting symptoms, adverse events, persistent rhinitis, sore throat, time off work and loss of appetite
Antibiotics for sore throat	Spinks A, Glasziou PP, Del Mar CB	November 2008	23 (7)	All studies: 12,835 (44–1,974) Children only: 1,929 (44–1,213)	All ages	Symptoms of sore throat	Any antibiotic	Placebo or any other antibiotic	Headache, fever, sore throat, and incidence of rheumatic fever, glomerulonephritis, otitis media and sinusitis or quinsy
Chinese medicinal herbs for sore throat	Shi Y, Gu R, Liu C, Ni J, Wu T, Yuan J	August 2006	7 (1)	All studies: 1,253 (80–400) Children only: 106	All ages	Sore throat, including acute or chronic pharyngitis, laryngitis or tonsillitis	Chinese medicinal herbs	Other Chinese medicinal herbs, other treatment or placebo	Recovery from sore throat, recovery from acute pharyngitis, inefficacy, change in TCM signs and adverse events
Delayed antibiotics for respiratory infections	Spurling GKP, Del Mar C, Dooley L, Foxlee R	March 2009	All studies: 10 (5) Sore throat only: 4 (2)	All studies: 2,691 (not stated) Sore throat and children only: 343 (114–229)	All ages	Any ARTI, including sore throat	Delayed antibiotics	Immediate antibiotics or no antibiotics	Pain, malaise, fever, cough, antibiotic use, patient satisfaction, re-consultation rate, use of alternate therapies and adverse events
Different antibiotic treatments for group A streptococcal pharyngitis	van Driel ML, De Sutter AIM, Keber N, Habraken H, Christiaens T	August 2010	17 (5)	All studies: 5,352 (96–919) Children only: 1,435 (162–525)	All ages	Symptoms of sore throat plus laboratory confirmed GABHS infection	Any antibiotic	Any other antibiotic	Resolution of symptoms, sore throat, fever, duration of illness, incidence of relapse, incidence of complications and adverse events

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Penicillin for secondary prevention of rheumatic fever	Manyemba J, Mayosi BM	June 2009	9 (3)	All studies: 3,008 (161–994) Children only: 1,011 (237–431)	All ages	History of rheumatic fever diagnosed using the original, modified or revised Jones criteria	Oral or intramuscular penicillin	Intramuscular penicillin or placebo	Rheumatic fever recurrence and streptococcal throat infection
Short versus standard duration antibiotic therapy for acute streptococcal pharyngitis in children	Altamimi S, Khalil A, Khalaiwi KA, Milner RA, Pusic MV, Al Othman MA	November 2007	20 (19)	All studies: 13,102 (96–4,782) Children only: 12,892 (96–4,782)	Children 1–18 years of age (one trial included participants up to 25 years)	Acute streptococcal pharyngitis diagnosed using rapid antigen testing or GABHS throat swab culture	Short-duration oral antibiotics (2–6 days)	Standard-duration oral antibiotics (ten days of penicillin)	Fever, sore throat, clinical efficacy, bacteriological efficacy, non-compliance, complications and adverse events
Steroids for symptom control in infectious mononucleosis	Candy B, Hotopf M	May 2008	7 (2)	All studies: 191 (24–86) Children only: 85 (40–45)	All ages	Documented clinical and laboratory diagnosis of glandular fever	Any steroid	Usual care or other active treatment	Duration and severity of sore throat, fever, fatigue, swallowing and pharyngeal secretions, and overall improvement in health

ARTI: acute respiratory tract infection; GABHS: group A beta-hemolytic streptococcus; TCM: traditional Chinese medicine; URTI: upper respiratory tract infection.

- Cephalosporins versus penicillin (two trials)
- Macrolides versus penicillin (one trial)
- Carbacephems versus penicillin (one trial)
- Immediate versus delayed antibiotics ('delayed antibiotics' refer to the advice from clinicians to caretakers to start using the antibiotics two days after the initial consultation) (two trials)
- Short-duration versus standard-duration antibiotics ('standard duration' refers to ten days of oral penicillin) (19 trials)
- Steroids versus placebo (two trials)
- Chinese herbal medicine (Ertong Qingyan Jiere Koufuye) versus Chinese herbal medicine (Fufang Shuanghua Koufuye) (one trial)

One review also examined administration of oral versus intramuscular penicillin (three trials) for the secondary prevention of rheumatic fever.

Outcome measures

Six of the included reviews specified primary outcomes (15, 30, 32–35). The most frequently reported primary outcomes were resolution of sore throat, fever, pain and overall symptoms (30, 32, 34). Other primary outcomes were inefficacy (15), persisting symptoms (33) and recurrence (but not initial occurrence) of rheumatic fever (35).

Methodological quality of included trials

Various instruments were used to evaluate the methodological quality of trials within each review, with one review (34) using more than one type of instrument. Four of the reviews (30–33) used the Cochrane Risk of Bias tool to assess trial quality based on sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias (i.e. study design or stopping early) (29). Based on the Risk of Bias criteria, 17% of trials in the four reviews were assessed as low risk of bias, 50% as unclear and 33% as high risk of bias.

Two reviews (34, 35) assessed the quality of allocation concealment to treatment groups (37). Together, these two reviews assessed allocation concealment as unclear in 38% of trials and inadequate in 62%. One of these reviews (34) also used the five-point Jadad scale to assess trial quality based on randomization technique, double-blinding procedure and documentation of losses to follow-up and withdrawals (38). The average Jadad score for the 19 pediatric trials was 2.4.

One review (15) assessed methodological quality using a published method based on generation of the allocation sequence, allocation concealment, double blinding and follow-up (39, 40). The one pediatric trial included in this review received a score of 'C' and was judged as having a high risk of bias because one or more of the above criteria were not met.

Lastly, one review (23) assessed trial quality based on allocation concealment, blinding and incomplete

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outcome data. Both included trials had adequate allocation concealment and incomplete outcome data reporting, and one of the two trials had adequate blinding.

Effects of interventions

Symptoms of sore throat

Table 2 presents data for sore throat, fever and overall symptoms. Data were available for eight different comparisons, and relevant results for each outcome are presented below.

Sore throat: The available data for sore throat examined length of sore throat, presence of sore throat, and pain due to sore throat, and data were obtained at 12 hours, day 1, day 3 and 6–8 days. Antibiotics did not decrease symptoms of sore throat at any time points when compared with placebo. Immediate compared to delayed prescription of antibiotics resulted in a 58% decrease in the number of participants with pain due to sore throat on day 3 (RR: 0.42; 95% CI: 0.33, 0.54), but did not significantly impact the severity of the pain. The number needed to treat (NNT) to prevent pain in one additional patient was 1.9 on day 3. Only one review (short versus standard-duration antibiotics) reported average duration of sore throat symptoms and found that a four-day course of cefuroxime axetil decreased sore throat symptoms by half a day when compared to ten days of oral penicillin (MD: −0.50; 95% CI: −0.78, −0.22). The review on Chinese herbal medicine measured symptoms of sore throat on day 3 and found that one type of herbal medicine (Fufang Shuanghua Koufuye) significantly decreased symptoms of sore throat compared to a second (Ertong Qingyan Jiere Koufuye) (RR: 1.40; 95% CI: 1.06, 1.85; NNT: 4.1). Steroids were better than placebo in decreasing sore throat symptoms in children with infectious mononucleosis; however, the difference was only statistically significant at 12 hours (RR: 0.54; 95% CI: 0.30, 0.99; NNT: 3.0) and the difference in symptoms between the two groups became progressively less at each of the three subsequent assessments.

Fever: Available outcomes for fever showed a similar pattern to the sore throat data. Antibiotics did not lead to a decrease in the number of children with fever on day 3 when compared to placebo. Immediate prescription versus delayed prescription did not impact fever severity on day 1 but led to a statistically significant yet moderate decrease in fever severity on day 3 (SMD: −0.53; 95% CI: −0.74, −0.31). Compared to ten days of oral penicillin, short-duration cephalosporins decreased the length of fever by seven hours (MD: −0.30; 95% CI: −0.45, −0.14).

Overall symptoms: Antibiotics compared to placebo did not significantly decrease presence of overall symptoms after seven days, and the choice of antibiotic regimen was not associated with the persistence of symptoms beyond the conclusion of treatment. Trials comparing cephalosporins, macrolides or carbacephem to oral penicillin found no significant differences in the time to resolution of overall symptoms.

Recovery, recurrence, sequelae and administrative outcomes

Table 3 presents data on recovery, recurrence, rheumatic fever, other sequelae, and administrative outcomes. Data were available for nine different comparisons, and relevant results for each outcome are presented below.

Recovery: Recovery was assessed using two outcomes: recovery from acute pharyngitis and return to normal activities after 1 week. Compared to the Chinese herbal medicine Ertong Qingyan Jiere Koufuye, 35% more participants receiving Fufang Shuanghua Koufuye recovered from acute pharyngitis (RR: 1.54; 95% CI: 1.01, 2.36; NNT: 4.4). There was no significant difference between steroids and placebo in infectious mononucleosis for return to normal activities after 1 week.

Recurrence: Short-duration antibiotics compared to standard-duration antibiotics did not significantly affect late clinical recurrence. Cephalosporins, macrolides and carbacephem were each compared to penicillin, and no statistically significant differences were found, although in one trial children receiving azithromycin were almost three times more likely to have late clinical recurrence than those receiving oral penicillin.

Rheumatic fever: In an analysis that included data from both adults and children, antibiotic treatment was found to be effective in the primary prevention of acute rheumatic fever (RR 0.27; 95% CI 0.12 to 0.60). Most of these trials used penicillin, and restricting the analysis to only these trials gave similar results. In our analysis using only the pediatric data, the risk ratio was comparable but the result was no longer statistically significant because of the very small number of cases of acute rheumatic fever in both the intervention and control groups (RR: 0.20: 95% CI 0.01, 4.18). More cases of acute rheumatic fever were noted in children receiving short versus standard-duration antibiotics, but these results also failed to reach statistical significance. In children with a past history of rheumatic fever, intramuscular penicillin compared to oral penicillin significantly reduced the recurrence of rheumatic fever by 92% (RR: 0.08; 95% CI: 0.04, 0.18), and the number needed to treat to prevent one recurrence of rheumatic fever was 6.2 patients.

Other sequelae: Children who received antibiotics (both oral and intramuscular) developed fewer cases of acute glomerulonephritis than those receiving placebo. However, the differences did not reach statistical significance, the number of events was small, and the confidence intervals were wide. There was also no statistically significant difference between short and standard-duration antibiotics in decreasing the number of participants who developed any sequelae (glomerulonephritis, acute rheumatic fever and suppurative

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Table II. Symptoms of sore throat

Symptom	Outcome	Comparison	Number of subjects (studies)	Measure of effect (95% CI)	I^2
Sore throat	Length of sore throat	**Short *vs* standard-duration antibiotics**	**188 (1)**	**MD: −0.50 (−0.78, −0.22)** [a]	—
	Sore throat at 12 hours	**Steroids *vs* placebo**	**39 (1)**	**RR: 0.54 (0.30, 0.99)** [b]	
	Sore throat on day 1	Steroids *vs* placebo	40 (1)	RR: 0.64 (0.37, 1.13)	—
	Sore throat on day 3	Any antibiotic *vs* placebo for sore throat	385 (2)	RR: 0.70 (0.25, 1.98)	98%
		CHM (Ertong Qingyan Jiere Koufuye) *vs* CHM (Fufang Shuanghua Koufuye)	**106 (1)**	**RR: 1.40 (1.06, 1.85)** [c]	—
		Steroids *vs* placebo	39 (1)	RR: 1.19 (0.37, 3.77)	—
	Pain due to sore throat on day 3	**Immediate *vs* delayed antibiotics**	**229 (1)**	**RR: 0.42 (0.33, 0.54)** [d]	—
	Pain severity due to sore throat on day 3	Immediate *vs* delayed antibiotics	114 (1)	MD: −0.30 (−0.75, 0.15)	—
	Sore throat at 6–8 days	Any antibiotic *vs* placebo for sore throat	344 (2)	RR: 1.39 (0.70, 2.75)	0%
		Any antibiotic *vs* placebo for common cold/acute rhinitis	188 (1)	RR: 0.91 (0.24, 3.53)	—
		Steroids *vs* placebo	39 (1)	RR: 1.05 (0.07, 15.66)	—
Fever	Length of fever	**Short *vs* standard-duration antibiotics**	**348 (2)**	**MD: −0.30 (−0.45, −0.14)** [a]	**0%**
	Fever severity on day 1	Immediate *vs* delayed antibiotics	343 (2)	SMD: 0.06 (−0.21, 0.33)	34%
	Fever severity on day 3	**Immediate *vs* delayed antibiotics**	**343 (2)**	**SMD: −0.53 (−0.74, −0.31)** [d]	**0%**
	Fever on day 3	Any antibiotic *vs* placebo for sore throat	61 (2)	RR: 1.27 (0.76, 2.13)	NA
Overall symptoms	Resolution of symptoms post-treatment	Cephalosporins *vs* penicillin	739 (2)	RR: 0.66 (0.25, 1.74)	80%
		Macrolides *vs* penicillin	489 (1)	RR: 1.15 (0.90, 1.46)	—
		Carbacephem *vs* penicillin	233 (1)	RR: 0.68 (0.47, 1.00)	
	Persisting symptoms after 7 days	Any antibiotic *vs* placebo for common cold/acute rhinitis	449 (2)	RR: 1.33 (0.57, 3.11)	0%
	Persistence of symptoms after treatment	Short *vs* standard-duration antibiotics	11541 (22)	RR: 0.86 (0.69, 1.08)	18%

[a] Significantly favours short-duration antibiotics; [b] Significantly favours steroids; [c] Significantly favours Fufang Shuanghua Koufuye; [d] Significantly favours immediate antibiotics.
CHM: Chinese herbal medicine; CI: confidence interval; MD: mean difference; NA: not applicable because one trial reported no events; RR: risk ratio; SMD: standardized mean difference.

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complications such as acute otitis media, sinusitis and peritonsillar abscess). In children with a past history of rheumatic fever, intramuscular versus oral penicillin led to a 78% reduction in number of participants who developed streptococcal throat infections (RR: 0.22; 95% CI: 0.17, 0.27) and the NNT was 1.8 patients; however, it should be noted that there was significant ($p = 0.005$) and substantial (I^2: 81%) heterogeneity for this outcome.

Administrative outcomes: The steroids review found no significant difference in the number of hospital admissions between participants receiving steroids or placebo. The delayed antibiotics review reported no significant difference on intention to re-consult between participants receiving delayed or immediate antibiotics.

Adverse effects

Table 4 presents data on adverse effects reported in all included reviews. Compared to participants receiving delayed antibiotics, those receiving immediate antibiotics showed a 93% reduction in vomiting (RR: 0.07; 95% CI: 0.03, 0.20). Participants receiving standard-duration antibiotics compared to short duration antibiotics showed a significant decrease in vomiting, diarrhea and abdominal pain (RR: 1.74; 95% CI: 1.31, 2.32). Lastly, individuals receiving penicillin experienced significantly fewer adverse events than those receiving macrolides (RR: 2.19; 95% CI: 1.04, 4.61). The numbers needed to treat to prevent the above listed adverse events were 2.2, 29.0 and 17.1 patients, respectively.

Discussion

Summary of main results

Effectiveness of antibiotics for children with sore throat

Results of both the antibiotic versus placebo and the delayed prescribing trials are relevant to this question. In the antibiotic versus placebo trials, there were no clinically relevant, statistically significant differences in fever or throat pain at three and seven days, although the confidence intervals for these comparisons do not exclude the possibility of a small benefit (or a small harm). Rates of adverse events were also similar, with no statistically significant differences for children receiving an antibiotic or placebo. Improvements in sore throat symptoms for delayed prescribing of antibiotics were small or undetectable. Children randomized to immediate versus delayed prescribing of antibiotics were less likely to have pain and fever on day three of their illness, while children randomized to delayed prescribing were more likely to experience vomiting (likely a symptom of their illness rather than an adverse effect of medication). This pattern of results is not dissimilar from that seen in systematic reviews that include data from both adults and children, in which antibiotics lead to a modest improvement in the severity and duration of symptoms but are also associated with small rates of adverse effects (41).

The possibility of sequelae such as suppurative disease requiring hospitalization, acute rheumatic fever or glomerulonephritis is of great concern to patients, parents and clinicians alike. In the placebo-controlled and delayed prescribing trials reviewed here, antibiotic use was not associated with a statistically significant reduction in sequelae. However, many of the included trials were of short duration and were designed to assess immediate outcomes rather than late sequelae. In addition, these severe outcomes are rare, leading to low event rates and wide confidence intervals that do not exclude the possibility of relatively large reductions in both glomerulonephritis and rheumatic fever with the use of antibiotics. However, even if antibiotics lead to a decrease in the occurrence of rare sequelae, it has been estimated that penicillins and cephalosporins are responsible for 18,000 pediatric emergency department visits each year in the USA (mostly due to allergic reactions), so this potential benefit of treatment must be weighed against the potential for adverse effects (42).

The probability of developing acute rheumatic fever is an important consideration in assessing the balance between potential benefits or harms of antibiotic therapy for a child with a sore throat. In areas where the incidence of acute rheumatic fever is very low – as in most high income countries – a child with an untreated streptococcal pharyngitis is unlikely to develop the disease. However, in settings where rheumatic fever occurs more frequently, a more liberal approach to the use of antibiotics would be appropriate, given the demonstrated effectiveness of penicillin in preventing this condition (43).

Choice of antibiotics

If the decision is made to prescribe an antibiotic for a child with sore throat, there is no good evidence from these reviews that any drug regimen is superior to the standard treatment of ten days of oral penicillin. While some studies showed small improvements in duration of symptoms with one regimen versus another, the differences are of little clinical importance. In two small trials, a short course of a newer antibiotic over a standard ten-day course of penicillin decreased length of sore throat by half a day and decreased duration of fever by seven hours. Although statistically significant, these results are of limited clinical relevance when factors such as cost of treatment and side effects are taken into account.

While no regimen is clearly better than oral penicillin, it should be noted that macrolides may be an inferior choice. In the trials included in this overview, children receiving a macrolide had more side effects and may have been more prone to recurrences. Macrolides are a particularly poor choice for

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Table III. Recovery, recurrence, sequelae and administrative outcomes

Category	Outcome	Comparison	Number of subjects (studies)	Measure of effect (95% CI)	I^2
Recovery	Recovery from acute pharyngitis	**CHM (Ertong Qingyan Jiere Koufuye) *vs* CHM (Fufang Shuanghua Koufuye)**	**106 (1)**	**RR: 1.54 (1.01, 2.36)** [a]	—
	Return to normal activities at 1 week	Steroid *vs* placebo	32 (1)	RR: 1.46 (0.72, 2.94)	—
Recurrence	Late clinical recurrence	Short *vs* standard-duration antibiotics	8068 (17)	RR: 1.06 (0.88, 1.27)	13%
		Cephalosporins *vs* penicillin	525 (1)	RR: 0.66 (0.11, 3.94)	—
		Macrolides *vs* penicillin	307 (1)	RR: 2.98 (0.67, 13.22)	—
		Carbacephem *vs* penicillin	154 (1)	RR: 1.50 (0.53, 4.27)	—
Rheumatic fever	Acute rheumatic fever	Short *vs* standard-duration antibiotics	5912 (1)	RR: 2.23 (0.12, 43.23)	—
		Any antibiotic *vs* placebo for sore throat	1330 (2)	RR: 0.20 (0.01, 4.18)	NA
	Rheumatic fever recurrence	**Intramuscular *vs* oral penicillin**	**869 (3)**	**RR: 0.08 (0.04, 0.18)** [b]	**0%**
Development of other sequelae	Acute glomerulonephritis	Short *vs* standard-duration antibiotics	7864 (2)	RR: 0.52 (0.06, 4.19)	0%
		Any antibiotic *vs* placebo for sore throat	1210 (1)	RR: 0.33 (0.01, 8.17)	—
	All sequelae*	Short *vs* standard-duration antibiotics	8135 (3)	RR: 0.55 (0.17, 1.81)	0%
	Streptococcal throat infections	**Intramuscular *vs* oral penicillin**	**869 (3)**	**RR: 0.22 (0.17, 0.27)** [b]	**81%**
Administrative outcomes	Hospital admissions	Steroid *vs* placebo	40 (1)	RR: 0.33 (0.04, 2.94)	—
	Intention to re-consult	Immediate *vs* delayed antibiotics	114 (1)	RR: 1.17 (0.50, 2.74)	—

[a] Significantly favours Fufang Shuanghua Koufuye; [b] Significantly favours intramuscular penicillin.
CHM: Chinese herbal medicine; CI: confidence interval; NA: not applicable because one trial reported no events; RR: risk ratio.
* Glomerulonephritis, acute rheumatic fever, and suppurative complications such as acute otitis media, sinusitis and peritonsillar abscess.

Table IV. Adverse effects

Outcome	Comparison	Number of subjects (studies)	Measure of effect (95% CI)	I^2
Vomiting	**Immediate *vs* delayed antibiotics**	**229 (1)**	**RR: 0.07 (0.03, 0.20)** [a]	—
Diarrhea	CHM (Ertong Qingyan Jiere Koufuye) *vs* CHM (Fufang Shuanghua Koufuye)	106 (1)	RR: 1.56 (0.07, 37.44)	—
Vomiting, diarrhea and abdominal pain	**Short *vs* standard-duration antibiotics**	**7997 (21)**	**RR: 1.74 (1.31, 2.32)** [b]	**58%**
Overall adverse events (unspecified)	Any antibiotic *vs* placebo for common cold/acute rhinitis	228 (2)	RR: 0.81 (0.32, 2.06)	35%
	Macrolides *vs* penicillin	**489 (1)**	**RR: 2.19 (1.04, 4.61)** [c]	—
	Carbacephem *vs* penicillin	233 (1)	RR: 0.80 (0.48, 1.32)	—

[a] Significantly favours immediate antibiotics; [b] Significantly favours standard-duration antibiotics; [c] Significantly favours penicillin.
CHM: Chinese herbal medicine; CI: confidence interval; RR: risk ratio.

adolescents with sore throat because of their ineffectiveness against *F. necrophorum*.

Use of corticosteroids

The Cochrane review on steroids only included trials assessing the use of corticosteroids for individuals with infectious mononucleosis. Only two small trials contained exclusively children, and only one of these reported on sore throat outcomes. However, the results in that one trial were consistent with the overall results in the Cochrane review (23). Corticosteroid use was associated with a small improvement in throat symptoms at 12 hours, but no benefits were seen beyond that time point. A recent non-Cochrane review (44) addressed the use of corticosteroids in patients with sore throat from other causes. The authors concluded that corticosteroids were effective in relieving sore throat pain, especially in the first 24 to 48 hours, and the effects were greatest for patients with severe or exudative pharyngitis. The trials in the review included both adults and children, and in their subgroup analyses of children only, the benefits did not reach statistical significance. All of the patients in all trials received antibiotics, so the authors were unable to draw conclusions about the effectiveness of corticosteroids prescribed as a sole agent.

Chinese herbal medicines

The authors of the Cochrane review on herbal medicines performed a careful and thorough search for evidence of effectiveness of Chinese herbal medicines of any type for patients with sore throat, but were unable to find any evidence of effective treatments. The review authors raised serious concerns about the quality of the trials they found, concluded that all of the trials were of methodologically poor quality, and recommended against the use of Chinese herbal preparations as therapy for sore throat (15).

Limitations of the overview

An initial challenge to this overview was the lack of clarity within the included reviews regarding ages of participants. Data for the majority of outcomes addressed in this overview were derived from a limited number of trials, often only one or two, with relatively small numbers of participants. This was a result of our focus on children only. When trials included a mixture of children and adults, we were only able to use the data if the Cochrane review included a sub-analysis of the results in children, which most did not. As a result, the number of trials and participants reported here are rather small, and few findings are statistically significant. Had we been able to review each trial individually, it may have been possible to extract additional information about the children in these trials. This could have resulted in improved precision in our estimates and may have resulted in statistically significant findings for some outcomes.

The evaluation of relative effectiveness of different antibiotic treatment regimens in the overview was based on only three reviews (30, 32, 34), all of which included only direct comparisons of antibiotic regimens. It is possible that better estimates could be obtained by a mixed treatment meta-analysis that included both direct and indirect comparisons.

There is a paucity of data on adverse events included in this overview. Most of the adverse events data that we do have is based on only one or two trials. Furthermore, many clinically important adverse events, such as rash and penicillin sensitization, are not included in this overview because the trials contained no relevant data. This is worrisome because lack of data does not necessarily mean that the interventions are safe. For example, approximately 0.7% of patients receiving penicillin will develop an allergic-like reaction within 30 days of treatment, and 0.6% of those will be anaphylactic reactions (45).

We were unable to conduct subgroup analyses based on the presence or absence of bacterial infection in children with sore throat because of variability in the way this issue was addressed in the included trials and reviews. For example, none of the included reviews used clinical decision rules like the Modified Centor Clinical Prediction Rule (8). Use of these tools, along with rapid antigen testing, might have resulted in significantly greater benefits of antibiotic use than our current data suggest, since some of the antibiotic-treated children may have had a viral or other non-bacterial cause for their sore throat.

Quality of the evidence

Although the included reviews followed the standard methods of *The Cochrane Collaboration*, there are serious concerns about the quality of many of the original trials. The authors of the review on Chinese herbal medications noted that there were significant methodological problems in all of the trials they were able to find. The quality of the trials in the other reviews was mixed: many trials had inadequate descriptions of allocation concealment, methods of randomization and blinding, and reasons for loss to follow-up. Since sore throat has been a longstanding topic of research interest, many of the trials were published before current reporting standards for trials were developed, and some of these defects may represent inadequate reporting rather than actual deficits in the methods used. However, the majority of trials were assessed by Cochrane authors as having a high or unclear risk of bias based on examination of their methodology, which clearly affects the strength of any conclusions which can be drawn from the extracted data.

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Authors' Conclusions

Implications for practice

This overview does not provide evidence in favour of the general use of corticosteroids or Chinese herbal medicine in the treatment of sore throat in children and adolescents. The use of antibiotics for sore throat involves a trade off between benefits and adverse effects. Data elsewhere may make a stronger case for antibiotic use when decision rules and rapid antigen testing are utilized. If antibiotics are prescribed, there is no evidence that newer antibiotics are significantly better than a standard ten-day course of oral penicillin, and there is some evidence that macrolides may lead to poorer outcomes.

Implications for research

There was a relative paucity of data comparing antibiotics with placebo in children, and trials of this type should be a priority. The development of more rapid and accurate means of distinguishing bacterial from viral infections in children presenting with sore throat should also be a priority. This would allow greater precision in the estimates from future trials assessing the effectiveness of antibiotics for children with sore throat of bacterial etiology, would make the management of this condition less problematic, and would likely reduce the rate of unnecessary antibiotic use.

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Contributions of Authors

All authors contributed to this overview. MF and LAB wrote the Background section, and MF extracted data, created results tables, and wrote the Methods and Results sections. LAB, BM and FD wrote the Discussion section, and LAB and BM wrote the Authors' Conclusions section. MF is the primary author of this report. All authors contributed to editing all sections of the overview and take responsibility for the manuscript.

Declarations of Interest

None.

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