Nebulised steroid in the treatment of croup: a systematic review of randomised controlled trials

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SUMMARY

Background. Croup is one of the commonest respiratory complaints among children. There is growing evidence that steroids may be an effective treatment.

Aim. To assess the effectiveness of treatment with nebulised steroid for children with croup.

Method. Systematic review of randomised controlled trials comparing administration of nebulised steroid with placebo. Trials were identified from searches of three bibliographic databases, the Cochrane Controlled Trials Register, correspondence with the manufacturers of nebulised steroid, and one round of manual citation searching.

Results. Eight randomised controlled trials were identified including 574 children with mild to severe croup. Overall, the mean age was 25.2 months and 72% of children were male. All trials were hospital-based and of good methodological quality, with adequate concealment of treatment allocation and blind outcome assessment. Children treated with nebulised steroid were significantly more likely to show an improvement in croup score by five hours (combined relative risk = 1.48, 95% confidence interval [CI] = 1.27 to 1.74) and significantly less likely to need hospital admission after attending the emergency department (combined relative risk = 0.56, 95% CI = 0.42 to 0.75) than the placebo group. The funnel plot indicated the presence of publication bias, with smaller studies showing the larger effects, but this could also be owing to less pronounced effects in studies of older children with milder croup.

Conclusions. Nebulised steroids are effective in the treatment of children attending hospital departments with croup. A meta-analysis based on individual patient data could clarify to what extent the effect depends on age and severity of disease. New trials are needed to define the indications for, and effectiveness of, steroid treatment of croup in the community.

Keywords: nebulised steroid; croup; randomised controlled trials.

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Introduction

ACUTE laryngotracheobronchitis, better known as croup, is one of the commonest respiratory complaints among children and the most common cause of airway obstruction in children aged six months to six years.[1,2] Although most children with croup recover without specific treatment, up to 15% require hospital admission, and, among those admitted, up to 5% may require intubation.[3,4]

Routine treatment with humidification, although traditional, is of no demonstrable benefit.[5,6] Nebulised adrenaline is effective but has a short duration of action and potentially dangerous side-effects, and is therefore not recommended for use in the community.[7-11] Oral and intramuscular steroid treatment, when given in adequate doses in hospital, has been shown to be effective for moderate to severe croup in a number of trials and a meta-analysis.[3,12] It has been suggested that nebulised administration is superior to the oral or intramuscular route because of a more rapid onset of action and fewer side-effects.[13,14] However, the effectiveness of nebulised steroid administration continues to be debated, with some studies showing significant benefit and others failing to do so. We systematically reviewed all placebo-controlled randomised trials of nebulised steroid in the treatment of croup and examined short-term effectiveness and hospital admission rates.

Method

Identification of relevant trials

We searched four electronic databases (MEDLINE, EMBASE, CINAHL, and the Cochrane Controlled Trials Register) from their year of inception. The search strategy was not limited by study design or language. The following terms were used: 'croup', 'laryngotracheobronchitis', 'steroid$', 'corticosteroid$', 'glucocorticoid$', 'dexamethasone', and 'budesonide' ('$' identifies all terms with the preceding stem). Bibliographies of the trials identified by these computerised searches were examined for further references to relevant randomised trials. Finally, information on any additional trials was requested from Astra Pharmaceuticals, the manufacturers of budesonide, who responded by searching data on file.

Inclusion criteria

We included all studies in which patients with croup (acute laryngotracheobronchitis or spasmodic) were randomly allocated to receive either nebulised steroid or saline placebo. Trials were included irrespective of the study setting, the diagnostic criteria used, and the severity of the symptoms. From over 300 published reports, one of the authors (SE) selected the abstracts of trials that potentially met our inclusion criteria. These abstracts were then assessed against the inclusion criteria by two pairs of authors (SG and SE or AFB and JR) independently.

Data extraction and outcomes

The following data were extracted from the published reports of each included trial onto standardised data collection forms independently by two authors (SG and SE): setting, patients' ages, baseline croup score (rating scales of severity of symptoms and

signs, such as respiratory rate and degrees of stridor and cyanosis, are detailed in Table 1), quality of allocation concealment, nature of the intervention, sample size, losses to follow-up, and the main outcomes measured in each study. Discrepancies were resolved by discussion.

Data on the following outcomes, where available, were extracted for treatment and placebo groups: the number of patients responding to treatment at five hours (defined as a croup score having decreased by two points or having a croup score of one or less) or at the time of hospital discharge if less than five hours, and the number of patients requiring hospital inpatient treatment after attending the emergency department (defined as admission to hospital up to seven days after treatment in the emergency department). Where data had been collected but were presented in a form that did not allow computation of these outcomes, the original investigators were contacted.

Statistical methods

A summary relative risk was calculated for the two outcomes from crude (unadjusted) data using a fixed-effects model and a chi-square test of between-trial heterogeneity was performed. Denominators for relative risk calculations were the number of subjects on whom outcome measure data had been collected. We used the relative risk rather than the odds ratio because the outcome (treatment response) occurred frequently and the odds ratio would therefore overestimate the relative risk.[15,16] The number needed to treat to prevent one hospital admission from the emergency department was derived from the risk difference for each trial.

Sensitivity analyses and investigation of heterogeneity

The analysis was repeated using a random-effects model to calculate overall estimates. A funnel plot was drawn to assess the possible influence of publication and location biases.[17] The asymmetry of the funnel plot, and hence the likelihood of bias, was quantified using the regression method described by Egger *et al*.[17] Finally, a multivariable regression analysis was performed to estimate the extent to which age, baseline croup score, and the standard error of the estimate explained heterogeneity in the response to treatment.[18]

We used the Cochrane Review Manager software[19] and Stata (Stata Corporation, College Station, Texas, USA) for data analysis. The test for publication bias was done using the Stata program Metabias,[20] while the regression analysis was done using the program Metareg.[21]

Results

The combined search strategies identified nine randomised trials involving nebulised steroid.[22-30] One of the trials did not meet the inclusion criteria as it evaluated nebulised budesonide against nebulised adrenaline rather than placebo.[30] The two pairs of authors independently selected the same eight trials for inclusion in the meta-analysis (Table 1). One trial had been published as a conference abstract; however, the authors provided the required additional data.[29] All eight trials meeting the inclusion criteria could thus be included. Unpublished data were also obtained for the trials by Godden[27] and Johnson.[28]

In aggregate, a total of 527 children not recently treated with steroids were randomly allocated to nebulised steroid or nebulised saline treatment. The overall mean of average ages was 25.2 months (range = 3 to 116); 72% were male. Entry criteria were broadly similar across studies, with all children being free from serious heart or lung complaints. Cases were defined on clinical grounds, the severity of croup ranging from mild to severe (average baseline croup score in the control group ranged

from 3.7 to 8.0, possible range = 0 to 17).

Trial quality

All eight trials were reported since 1993 and were of good methodological quality. The procedures to ensure adequate allocation concealment (at randomisation and outcome assessment) were well described, groups were well matched at baseline, and losses to follow-up were few (11.0% overall). Six of the eight studies reported sample size calculations.[22,23,25,26,28,29]

Response to treatment

As shown in Figure 1, trials produced similar effect sizes favouring nebulised steroid, with little evidence of heterogeneity (χ^2 = 7.47, P = 0.41). Children were one-and-a-half times more likely to demonstrate a clinically significant improvement within five hours if treated with nebulised steroid (combined relative risk = 1.48, 95% confidence interval [CI] = 1.27 to 1.74).

Hospital admission

Five of the studies were set in emergency departments and reported data for subsequent hospital admission.[23-26,28] Effect sizes exhibited slightly greater heterogeneity than for response to treatment (Figure 2) although not achieving conventional levels of significance (χ^2 = 5.24, P = 0.30). Children were significantly less likely to require admission in the treatment compared with the placebo group (relative risk = 0.56, 95% CI = 0.42 to 0.75). The number of children needing nebulised steroid treatment in the emergency department to prevent one hospital admission ranged from 2.9[28] to 8.4.[25]

Sensitivity analysis and investigation of heterogeneity

Use of a random rather than fixed-effects model made little difference to overall estimates. The funnel plot (Figure 3) shows seven trials clustered around the overall estimate of effect size, with one outlying trial generating significant asymmetry. This was confirmed by the coefficient from univariable regression analysis[17] (2.95; 95% CI = 1.50 to 4.41, P = 0.003). However, when we included age and severity in a multivariable model, this coefficient was reduced and became non-significant (2.52; 95% CI = -1.05 to 6.10, P = 0.17).

Discussion

Based on eight randomised controlled trials, this systematic review indicates that treatment with nebulised steroid in hospital rapidly alleviates symptoms in children with mild to severe croup and prevents subsequent hospital admissions, with one admission prevented for every three to eight children treated in the emergency department. Trials were generally of good quality with adequate concealment of treatment allocation and blind outcome assessment. Five out of eight trials showed a statistically significant effect on symptom scores.

The croup scores that were used in the trials have been shown to be valid and reliable,[25,26,31] yet they differ in the clinical parameters assessed and hence may vary in sensitivity and responsiveness. It is unlikely that this biased our findings as scores were assessed blindly in the original trials; also, they were not used directly in this review but were re-coded into a clinically relevant response to treatment.

Publication and related biases

Systematic reviews and meta-analyses based on a few small trials should be interpreted with caution.[17] 'Negative' trials showing no significant treatment effect are less likely to be published

Table 1. Characteristics of trials included in the meta-analysis

Reference	Setting	Randomisation and allocation concealment	Inclusion criteria[a]	Exclusion criteria	n	Losses to follow-up	Intervention	Main outcome measures
Husby[22] 1991	Hospital paediatric department, Denmark	Random numbers, double-blind at intervention and outcome assessment	Age = 0.25–4.9 years (median = 1.1, range = 0.4–4.2), moderate to severe croup, score >5 (median = 8, range = 6–12, possible range = 0–17)	Foreign body, bronchiolitis, asthma, steroid, or adrenaline treatment	37	1	1000 mg nebulised budesonide, repeated after 30 minutes	Change in croup score (stridor, cough, retractions, dyspnoea, cyanosis) and overall disease severity after 2 hours
Klassen[26] 1994	Emergency department, Children's Hospital, Ontario, Canada	Random number tables in blocks of 10 by pharmacy, double-blind at intervention and outcome assessment (opaque nebules)	Age 0.25–5 years (mean = 2.2, SD = 1.4), mild to moderate croup, score ≥2 and <8 (median = 4, IQR = 3–5, possible range = 0–17)	Epiglottitis, chronic airway disease except asthma, steroid treatment within 2 weeks	54	0	2000 mg nebulised budesonide	Croup score (stridor, retractions, air entry, cyanosis, conscious level), general condition (Likert scale), duration of stay in emergency department
Geelhoed[24] 1995	Emergency department, Children's Hospital, Perth, Australia	Method of randomisation not specified, double-blind at intervention	Age >0.25 years (mean = 2.5, SD = 1.92), moderate croup, score ≥3 (mean = 3.8, possible range = 0–6)	Pre-existing upper airway condition, poor English, no telephone, steroid treatment within 1 week, severe croup, admitted to ITU	57	9	2000 mg nebulised budesonide	Duration of hospitalisation, use of nebulised adrenaline, croup score (stridor, retractions)
Johnson[25] 1996	Emergency department, Children's Hospital, Ontario, Canada	Randomised in blocks of 10 by pharmacy, double-blind at intervention and outcome assessment (opaque nebules)	(Median age = 1.42 years, IQR = 0.75 to 1.83). Mild to moderate croup, score = 2.5–5 (median = 4, IQR = 3–4, possible range = 0–17)	Steroid treatment within 1 week, adrenaline within 4 hours, spasmodic croup, severe asthma, congenital stridor, intubation for >1 month	55	0 (2 hours) 17 (4 hours)	10 mg (<8 kg body weight) 15 mg (8–12 kg) 20 mg (>12 kg) nebulised dexamethasone	Croup score (stridor, retractions, air entry, cyanosis, conscious level) at 4 hours, hospital admission
Klassen[23] 1996	Emergency department, Children's Hospital, Ontario, Canada	Random number tables in blocks of 10 by pharmacy, double-blind at intervention and outcome assessment (opaque nebules)	Age = 0.25–5 years (mean = 1.2, SD = 0.7), mild to moderate croup, score ≥3 and <8 (mean = 4.4, SD = 1.1, possible range = 0–17)	Epiglottitis, chronic airway disease except asthma, steroid treatment within 2 weeks	50	1 (at 1 week)	Oral dexamethasone (0.6 mg/kg) to both groups + 2000 mg nebulised budesonide	Proportion with 2-point decrease in croup score (stridor, retractions, air entry, cyanosis, conscious level) within 4 hours, hospital admission
Godden[27] 1997	Hospital paediatric ward, Poole, England	Randomised by manufacturer, double-blind at intervention and outcome assessment (opaque nebules)	Ward admissions (mean age = 3.12 years, range = 0.58–7.8) (mean croup score = 5.15, SD = 3.7, possible range = 0–17)	Steroid treatment within 1 week, bronchodilator treatment,	95	13	2000 mg nebulised budesonide, 1000 mg given 12-hourly	Croup score (oxygen saturation, stridor, cough, recessions, respiratory distress), length of hospital stay

[a]Age and baseline croup scores are for placebo group. IQR = interquartile range (continued on next page).

Table 1 (cont). Characteristics of trials included in the meta-analysis

Reference	Setting	Randomisation and allocation concealment	Inclusion criteria[a]	Exclusion criteria	n	Losses to follow-up	Intervention	Main outcome measures
Roberts[29] 1998	Infectious disease ward, Adelaide, Australia	Randomised in blocks of 10 by manufacturer, double-blind at intervention and outcome assessment (opaque nebules)	Age = 0.5–8 years (mean = 2.2, SD = 1.0). Moderate to severe croup, score ≥4 (mean = 6.3, SD = 1.4, possible range = 0–11)	Intubation within 1 year, steroids within 4 weeks or adrenaline within 1 week, epiglottitis, foreign body, bronchiolitis, pneumonia, asthma	82	4 (2 hours) 16 (3 days)	2000 mg nebulised budesonide, repeated every 12 hours	Croup score (stridor, retractions, dyspnoea, tachypnoea, cyanosis), time to clinical improvement, further medical help sought
Johnson[28] 1998	Emergency departments of two Canadian paediatric hospitals (Calgary and Toronto)	Block randomisation by manufacturer using random number software, double-blind at intervention and outcome (opaque nebules)	Age = 0.25–9 years (mean = 2.0, SD = 1.5), moderate croup, score = 3–6 (mean = 3.8, SD = 0.8, possible range = 0–17)	Stridor/intubation for >1 month, steroids within 1 month, chronic pulmonary or severe systemic disease, immune dysfunction, epiglottis, bacterial tracheitis, foreign body, poor English	144	1 (after discharge)	0.5 ml, 2.25% racemic epinephrine and either 4000 mg nebulised budesonide (48), 0.6 mg/kg intramuscular dexamethasone (47) or placebo (49)	Hospitalisation rates, croup score, respiratory rate, heart rate, blood pressure, oxygen saturation, additional epinephrine treatments

[a]Age and baseline croup scores are for placebo group. IQR = interquartile range.

in indexed journals,[32] less likely to be published in English,[33] and less likely to be cited by other authors.[34] These trials are therefore also less likely to be identified for, and included in, systematic reviews. Such publication, language, or citation biases are more likely to affect small studies rather than larger multi-centre trials, which tend to be published in English and cited irrespective of their results. Small trials also tend to be of lower methodological quality, which has been shown to be associated with larger effects.[35] The asymmetrical funnel plot, with the largest trials[27,28] producing the smallest effects, indicates that bias may have distorted our review. However, seven of the eight studies produced similar effects (relative risks from 1.22 to 1.90), and differences between the trials with outlying results other than sample size could also explain the asymmetry. The trial with the oldest children[27] produced a much smaller effect than the trial with the youngest, which also included children with a high croup score.[22] This is not surprising given the close relationship between age, airway diameter, and croup symptoms.[36,37] In multivariate analysis it became evident that the variation between trials in the subjects' ages and croup severity may indeed account for the apparent effect of sample size. A meta-analysis based on individual patient data could more precisely examine to what extent treatment effects depend on age and disease severity.[38]

Choice of steroid

An earlier meta-analysis,[12] a subsequent trial,[24] and the present systematic review indicate that both oral and nebulised steroid therapy are effective. Some authors have argued that nebulised steroid may work more quickly than the oral version (which is supported by animal studies[39]) and has fewer systemic side-effects,[13,14] although such side-effects are rare.[3,12] However, few studies have directly compared different steroids and routes of administration. A small trial that compared oral dexamethasone and nebulised budesonide found no significant differences in short-term response and duration of hospitalisation.[24] In another study, children who received oral dexamethasone appeared to benefit from additional treatment with nebulised budesonide.[23] The results from the most recent trial indicate that intramuscular dexamethasone reduces croup scores and hospital admissions more effectively than nebulised budesonide.[28]

The previous meta-analysis also demonstrated a dose-response relationship for systemic glucocorticoids.[12] This was not evident in this review of trials of nebulised treatment. Neither administration of 4000 µg rather than 2000 µg of budesonide, nor repeated treatment every 12 hours, were associated with increased effect sizes.

We are not aware of any trials that were conducted in primary care, hence the optimal treatment strategy for general practice remains unclear. Family doctors may be more comfortable using a topical treatment to which they have ready access, for what, in the majority, of cases is likely to be a self-limiting illness. On the other hand, a distressed child may be more comfortable with the oral version.[24] Another consideration is cost: nebulised steroid is considerably more expensive than the oral or intramuscular versions (2000 µg of budesonide costs £4.46).[40]

Generalisability

All the studies took place in the hospital setting where croup is now routinely treated with steroids in one form or another.[41] No such consensus exists for general practice,[1] and, although children with relatively mild croup and correspondingly low croup scores were included in three of the trials, the evidence presented suggests that the effect may be more pronounced in moderately severe and severe cases. The appropriate threshold for steroid
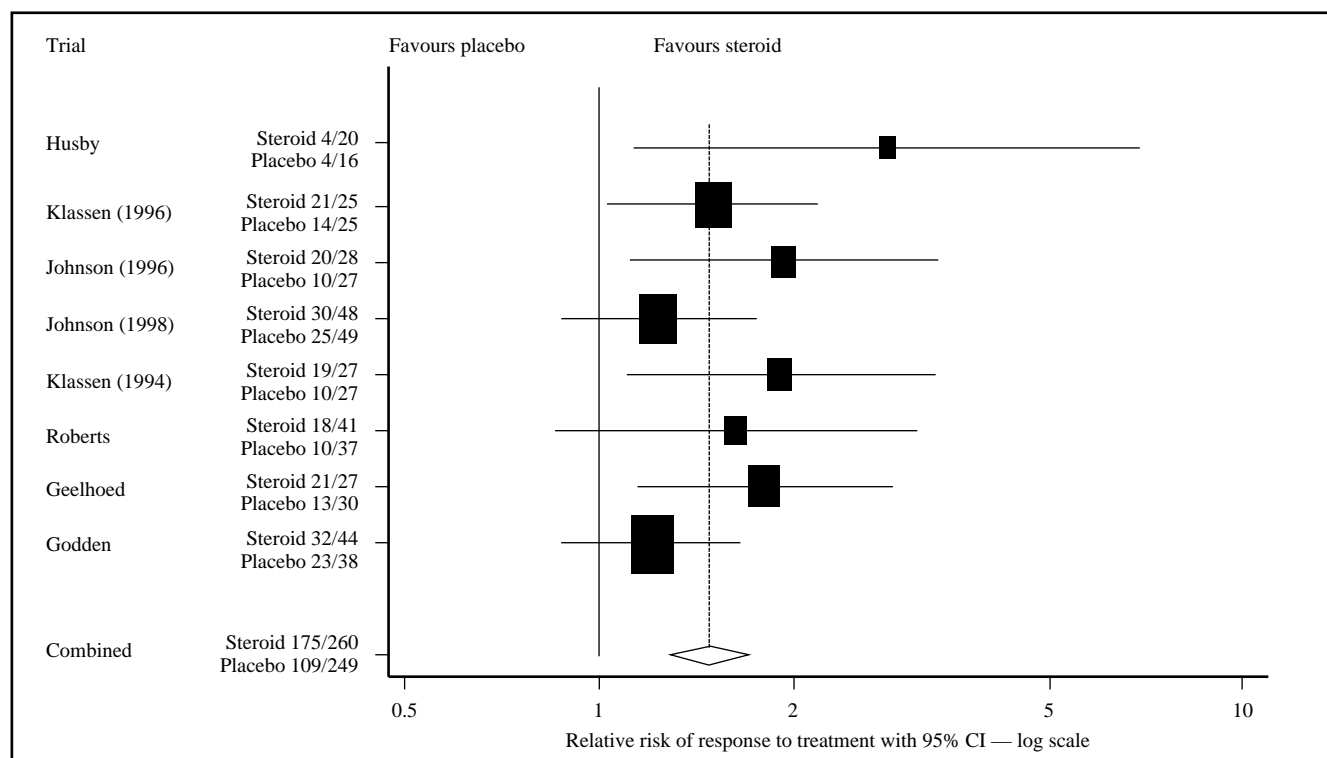
Figure 1. Relative risk of response to treatment (individual trials are plotted on the *y*-axis in order of decreasing average age of children at baseline).
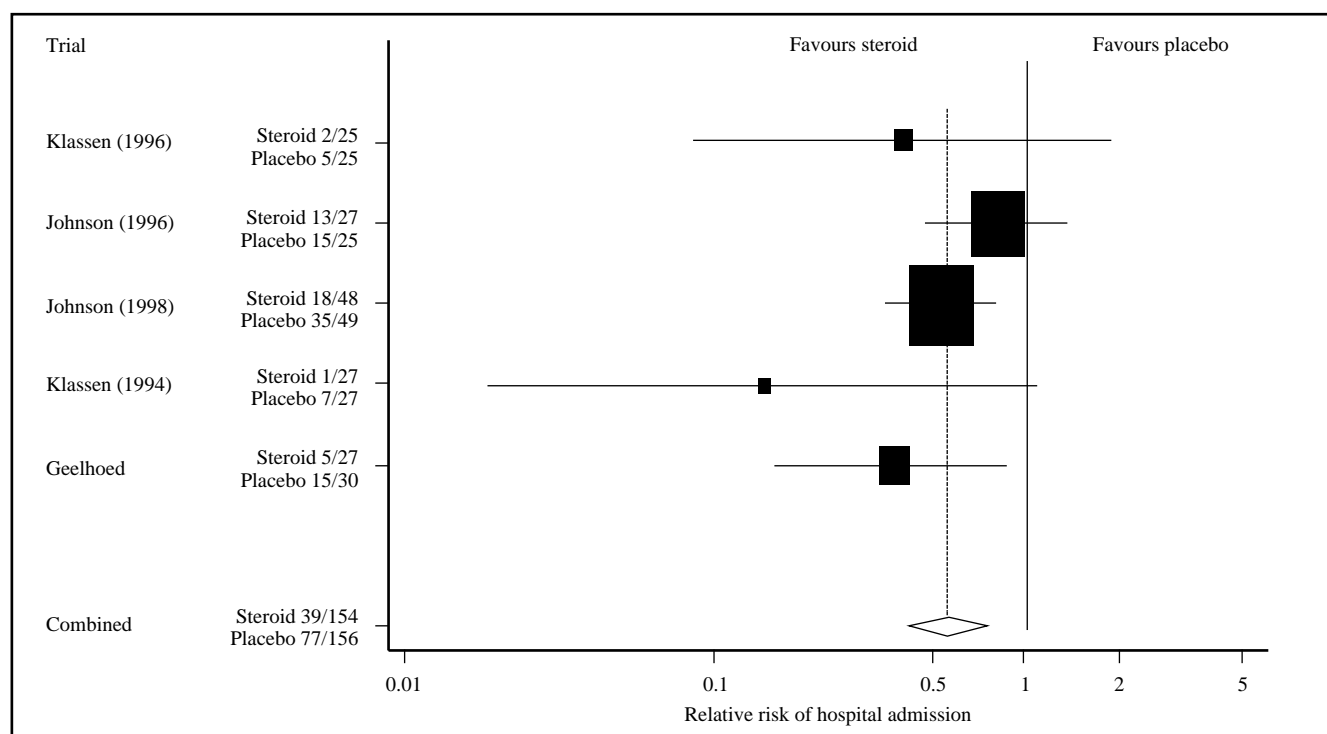
Figure 2. Relative risk of hospital admission.

treatment for croup in general practice is not known. It is possible that steroid treatment at an early stage in the community may attenuate the course of the condition in some children and ultimately reduce costs to the child, the family, and the health service by preventing hospital admissions. However, any such benefits

need to be assessed against, not only the immediate costs, but also against the risk of medicalising croup in the long term[42,43] and the risks of management at home without access to respiratory support. A randomised trial is needed to answer these questions and inform the use of steroid treatment for croup in general practice.
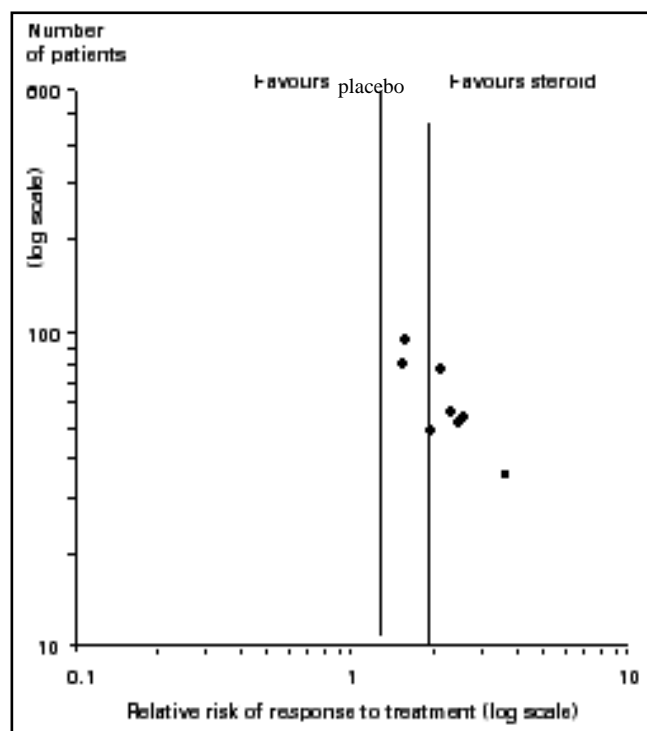
Figure 3. Funnel plot of relative risks of response to treatment against number of children in trial.

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