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Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma (Review)

Cates CJ, Welsh EJ, Rowe BH

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TABLE OF CONTENTS

[Intervention Review]

Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

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ABSTRACT

Background

In acute asthma inhaled beta² -agonists are often administered by nebuliser to relieve bronchospasm, but some have argued that metered-dose inhalers with a holding chamber (spacer) can be equally effective. Nebulisers require a power source and need regular maintenance, and are more expensive in the community setting.

Objectives

To assess the effects of holding chambers (spacers) compared to nebulisers for the delivery of beta² -agonists for acute asthma.

Search methods

We searched the Cochrane Airways Group Trial Register and reference lists of articles. We contacted the authors of studies to identify additional trials. Date of last search: February 2013.

Selection criteria

Randomised trials in adults and children (from two years of age) with asthma, where spacer beta² -agonist delivery was compared with wet nebulisation.

Data collection and analysis

Two review authors independently applied study inclusion criteria (one review author for the first version of the review), extracted the data and assessed risks of bias. Missing data were obtained from the authors or estimated. Results are reported with 95% confidence intervals (CIs).

Main results

This review includes a total of 1897 children and 729 adults in 39 trials. Thirty-three trials were conducted in the emergency room and equivalent community settings, and six trials were on inpatients with acute asthma (207 children and 28 adults). The method of

delivery of beta² -agonist did not show a significant difference in hospital admission rates. In adults, the risk ratio (RR) of admission for spacer versus nebuliser was 0.94 (95% CI 0.61 to 1.43). The risk ratio for children was 0.71 (95% CI 0.47 to 1.08, moderate

quality evidence). In children, length of stay in the emergency department was significantly shorter when the spacer was used. The mean duration in the emergency department for children given nebulised treatment was 103 minutes, and for children given treatment via spacers 33 minutes less (95% CI -43 to -24 minutes, moderate quality evidence). Length of stay in the emergency department for adults was similar for the two delivery methods. Peak flow and forced expiratory volume were also similar for the two delivery methods. Pulse rate was lower for spacer in children, mean difference -5% baseline (95% CI -8% to -2%, moderate quality evidence), as was the risk of developing tremor (RR 0.64; 95% CI 0.44 to 0.95, moderate quality evidence).

Authors' conclusions

Nebuliser delivery produced outcomes that were not significantly better than metered-dose inhalers delivered by spacer in adults or children, in trials where treatments were repeated and titrated to the response of the participant. Spacers may have some advantages compared to nebulisers for children with acute asthma. The studies excluded people with life-threatening asthma; therefore, the results of this meta-analysis should not be extrapolated to this patient population.

PLAIN LANGUAGE SUMMARY

Holding chambers (spacers) versus nebulisers for delivery of beta-agonist relievers in the treatment of an asthma attack

Review question

When someone is having an asthma attack is it as safe and effective to use a spacer instead of a nebuliser?

Background

During an asthma attack, the airways (tubes in the lungs) narrow making breathing difficult. The initial response to an asthma attack is to treat with a drug that can open up the airways and make breathing easier. These drugs are called bronchodilators and in this review we are looking specifically at a class of bronchodilators called beta-agonists (for example salbutamol). These drugs can be taken straight from an inhaler, but during an asthma attack they are easier to take using either a spacer or a nebuliser. A spacer is a hollow chamber. A puff of drug from an inhaler is added to the chamber and then the person breathes in and out normally (also described as tidal breathing), from a mouthpiece on the chamber. A nebuliser is a machine with a mask that goes over the person's mouth and nose and through which a constant stream of drug and air (or oxygen) is breathed in and out normally.

What evidence did we find?

We found 39 clinical trials involving 1897 children and 729 adults. Thirty-three of the trials were conducted in an emergency room (or emergency department) and community settings (such as a GP's surgery), and six trials were on inpatients (people in hospital) with acute asthma (207 children and 28 adults). Overall we judged the quality of the evidence to be moderate.

What do the studies tell us?

Taking beta-agonists through either a spacer or a nebuliser in the emergency department did not make a difference to the number of adults being admitted to hospital, whilst in children we can be fairly confident that nebulisers are not better than spacers at preventing admissions.

In children, the length of stay in the emergency department was significantly shorter when the spacer was used instead of a nebuliser. The average stay in the emergency department for children given nebulised treatment was 103 minutes. Children given treatment via spacers spent an average of 33 minutes less.

In adults, the length of stay in the emergency department was similar for the two delivery methods. However the adult studies were conducted slightly differently which may have made it more difficult to show a difference in the length of stay in the emergency department. Because all the adult studies used a so-called "double-dummy" design, the adults received a spacer AND a nebuliser (either beta-agonist in a spacer and a dummy nebuliser or vice versa) which meant both groups of people were in the emergency department for as long as it took to take both treatments.

Lung function tests were also similar for the two delivery methods in both adults and children. Pulse rate was lower in children taking beta-agonists through a spacer (mean difference -5% baseline), and there was a lower risk of developing tremor.

Conclusion

Metered-dose inhalers with a spacer can perform at least as well as wet nebulisation in delivering beta$_2$ -agonists in children with acute asthma, but we are less certain about the results in adults.

The review is current as of February 2013.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Multiple treatment of beta$_2$ -agonist via spacer (chamber) compared to nebuliser for children with acute asthma

Patient or population: children with acute asthma
Settings: Community or Emergency Department
Intervention: Multiple treatments with beta$_2$ -agonist via spacer (chamber)
Comparison: Multiple treatments with beta$_2$ -agonist via nebuliser

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Nebuliser	Multiple treatment of beta$_2$-agonist via spacer (chamber)				
Hospital admission	**110 per 1000**	**78 per 1000** (52 to 119)	**RR 0.71** (0.47 to 1.08)	757 (9 studies)	⊕⊕◯◯ **low**[1,2]	Large increases in the proportion of children admitted to hospital on spacer in comparison to nebuliser are ruled out by this 95% confidence interval
Duration in emergency department (minutes)	The mean duration in emergency department (minutes) in the control groups was **103 minutes**	The mean duration in emergency department (minutes) in the intervention groups was **33 minutes shorter** (43 minutes shorter to 24 minutes shorter)		396 (3 studies)	⊕⊕⊕◯ **moderate**[1]	There was a consistent direction of shortening of time in ED in all 3 studies, and although the size of this effect varied between studies (I^2 = 66%), we felt that the mean difference was important in all studies

Final rise in FEV_1 (% predicted)	The mean final rise in FEV_1 (% predicted) in the control groups was **27% predicted at baseline**	The mean final rise in FEV_1 (% predicted) in the intervention groups was **0.92% higher** (4.96% lower to 6.79% higher)		48 (2 studies)	⊕⊕◯◯ **low**[1,2]
Rise in pulse rate (% baseline)	The mean rise in pulse rate (% baseline) in the control groups was **7% rise from baseline**	The mean rise in pulse rate (% baseline) in the intervention groups was **5.62% lower** (7.52% to 3.72% lower)		670 (9 studies)	⊕⊕⊕◯ **moderate**[1]
Number of participants developing tremor	**142 per 1000**	**91 per 1000** (62 to 135)	**RR 0.64** (0.44 to 0.95)	254 (4 studies)	⊕⊕⊕◯ **moderate**[1]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Mostly open label studies
[2] Wide confidence intervals

BACKGROUND

Description of the condition and intervention

Exacerbations of asthma are common and account for a considerable number of physician encounters, both in hospital and in primary care. In exacerbations the airways become narrowed due to mucosal oedema, hypersecretion and bronchospasm. Depending on the severity of the attack, treatment with inhaled beta^2 -agonists is often required in addition to other agents such as corticosteroids. The use of beta^2 -agonists is intended to relieve the bronchospasm. This is accomplished most effectively when the drug is delivered to the peripheral airways. This is made more difficult in acute asthma since the narrowed airways and faster respiratory rate result in increased drug deposition in the throat and large airways. Consequently, it is less effective and may cause more side effects. Two different delivery methods have been employed to overcome this problem: wet nebulisations and metered-dose inhalers (MDIs) with a holding chamber (spacer). Nebulisation creates a mist of beta^2 -agonist diluted in saline which is inhaled through a mask by tidal breathing. Nebulisation can be accomplished with room air or supplemental oxygen, and requires a supply of compressed gas or a power source. More recently, beta^2 -agonists delivered via MDIs through a spacer have been used in acute asthma. The drug is released into the spacer by pressing the MDI after it has been shaken and inserted into the spacer (also called 'actuation'). The drug in the spacer is then emptied by the person using either tidal breathing (normal breathing in and out) or a single deep breath.

Why it is important to do this review

Whilst nebulisers have historically been used in exacerbations of asthma, a meta-analysis of trials in adults with asthma or chronic obstructive pulmonary disease (COPD) suggested that metered-dose inhalers with a spacer are as effective (Turner 1997).There has been considerable controversy regarding the merits of each delivery method, but current guidelines have now moved towards the use of spacers in acute asthma, particularly in children (BTS/SIGN 2011). In addition, cost and infection control considerations may be important additional determinants of which system is employed. For example, in the community the cost of nebulisers exceeds a spacer and MDI. In hospital emergency departments, the cost calculations are more complex since disposable nebuliser masks are often driven by piped oxygen; costs may depend on whether or not all patients are sent home with a new spacer. Nebulisers also represent a potential source of cross-infection, and require regular maintenance. As a result of these controversies, this systematic review has been updated to assess all the available evidence from randomised controlled trials comparing the two delivery methods in adults and children with acute asthma.

OBJECTIVES

To assess the effects of holding chambers (spacers) compared to nebulisers for the delivery of beta^2 -agonists for acute asthma.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials were considered for this review.

Types of participants

Adults and children (but not infants) with acute asthma presenting for medical assistance in the community setting or hospital emergency department. Studies describing people who had already been admitted to hospital have been included in this update. Studies of children with a mean age of two years or more were included, as it is difficult to diagnose asthma under this age. Studies of people with asthma and chronic obstructive pulmonary diease (COPD) were included as long as separate results could be obtained for the asthma patients.

Types of interventions

Any beta^2 -agonist given by any nebuliser versus the same beta^2 -agonist given by metered-dose inhaler with any spacer. The dose of drug and method of administration must have been recorded. Co-interventions and contamination (cross-over) may have occurred, but these must have been recorded.

Types of outcome measures

Primary outcomes

1. Admission to hospital.
2. Duration of hospital stay for inpatients.

Secondary outcomes

1. Duration in the emergency department.
2. Change in respiratory rate.
3. Blood gases.
4. Pulse rate.
5. Tremor.
6. Symptom score.
7. Lung function.
8. Use of steroids.
9. Relapse rates.

Search methods for identification of studies

Electronic searches

We identified trials using the Cochrane Airways Group Specialised Register, which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). All records in the Specialised Register coded as 'asthma' were searched using the following terms:
(spacer* OR "holding chamber*" or holding-chamber* OR volumatic OR nebuhaler* OR aerochamber* OR fisonair OR extension* OR "spacing device*" OR inspirease OR babyhaler* or MDI or turbuhaler) AND (nebuli*)
The most recent search of the Register was carried out in February 2013.

Searching other resources

We searched the bibliographies of all included papers and reviews for further references. We contacted authors of included studies for identification of any unpublished or missed trials.

Data collection and analysis

Selection of studies

One review author (CJC) originally checked abstracts identified by the above search and obtained the full text of publications of possibly relevant studies, including translation when required. Trials identified for potential inclusion were independently assessed by one review author (CJC) and William Griffiths, a student at St George's University of Londonfor the present update.

Data extraction and management

CJC extracted data and JAC checked them. They contacted trial authors by letter asking for clarification of allocation concealment, devices used, location of the participants and outcomes where these were not clear in the original publication.

Assessment of risk of bias in included studies

Two people (CJC, and William Griffiths or EW) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion. We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low or unclear, and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' tables. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a participant-reported pain scale).

Assessment of heterogeneity

Heterogeneity was originally measured using the Chi² test and latterly the I² statistics for more recent updates. Where heterogeneity was found, we explored sources of heterogeneity and pooled results using a random-effects model, or did not pool across subgroups.

Data synthesis

We calculated a weighted treatment effect across trials using the Cochrane statistical package, Review Manager (RevMan; initially version 4, now 5.2). Results are expressed as risk ratios (RR) and a 95% confidence interval (CI) for dichotomous outcomes and mean differences (MD) and a 95% CI for continuous outcomes. We used a fixed-effect model for continuous outcomes, but also checked results using a random-effects model.
We have now separated the results for adults and children in each outcome, in view of the significant heterogeneity identified in the pooled analyses. Furthermore it can be argued that adults and children may differ in their ability to use the devices, their degree of airways reversibility and in their sensitivity to side effects from inhaled beta^2 -agonists.

We have not pooled the single-treatment trials because of concerns over confounding due to uncertainty about the relative dose delivered and the wide range of dose-ratios used (from 1:1 to 1:13, with the larger doses administered via nebuliser).

Sensitivity analysis

We performed sensitivity analyses on the basis of methodological quality. The results were originally re-analysed using only studies of the lowest risk of bias. Sensitivity analyses were performed to check on the effect of estimating standard deviations and the data re-analysed without any estimated results. In addition, we generated a funnel plot of hospital admissions to check for publication bias. In view of the temporary discontinuation of Volumatic spacers in some countries, we also separated the trials that used Volumatic from other types of spacer in an additional post hoc subgroup analysis.

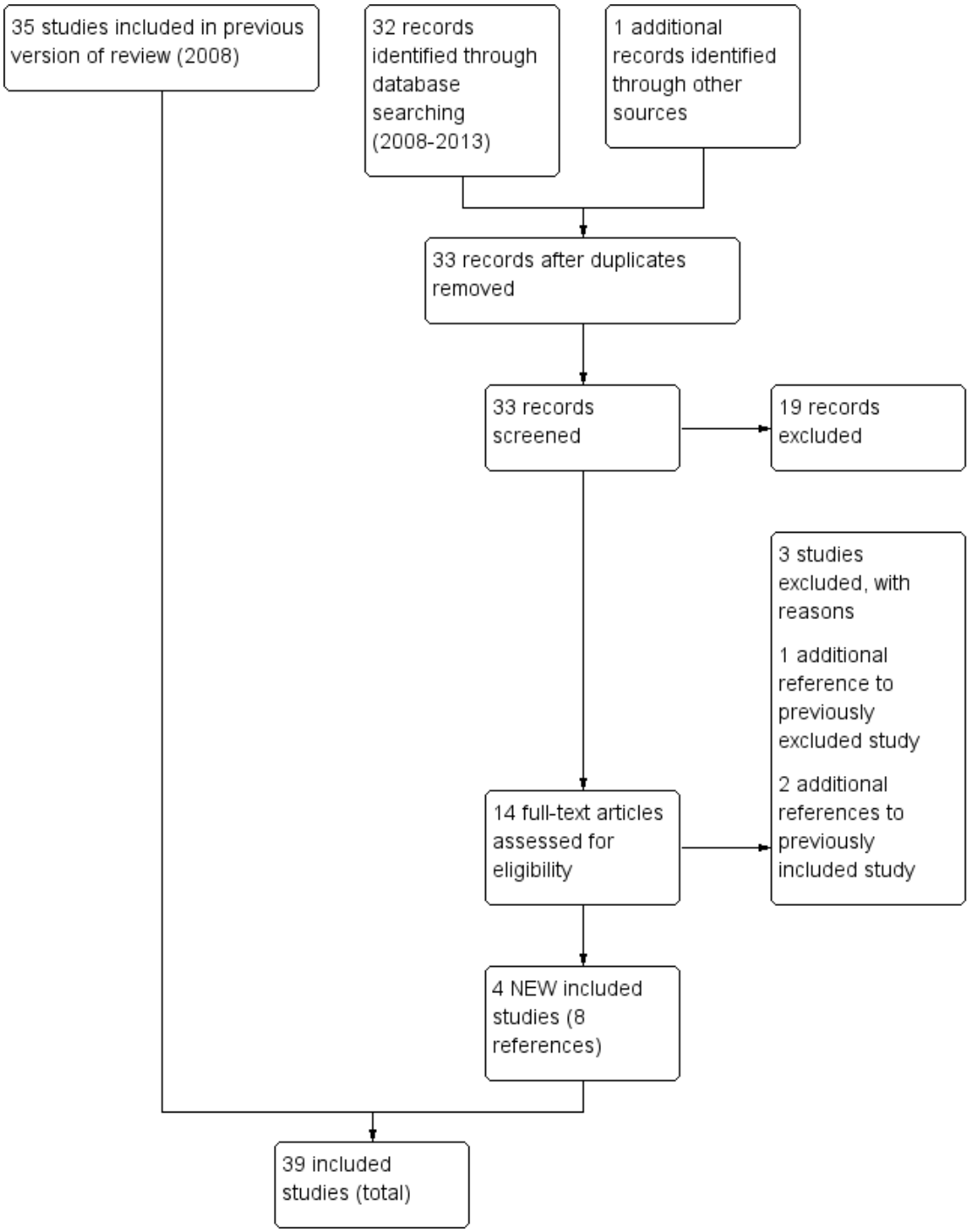
RESULTS

Description of studies

Results of the search

There were 35 included studies previously identified by literature searches conducted up to 2008. For this review update, our literature search covered the period 2008 to 2013 (see Figure 1 for details). We have included four new trials (Dhuper 2008; Direkwatanachai 2008; Ferrés 1989; Yasmin 2012), and have excluded three (Fayaz 2009; Hart 2009; Kaashmiri 2010).

Figure 1. Study flow diagram



Included studies

See Characteristics of included studies tables for full details.

There are now 1203 children (in 15 trials) and 613 adults (in 10 trials) who were randomised to spacer or nebuliser using multiple-treatment protocols. There are also 487 children (in six trials) and 88 adults (in two trials) who were randomised to a single-treatment regimen. In addition there are six trials incorporating 207 children and 28 adults studied after hospital admission. Table 1 gives details of the location and design of each study, as well as the type of spacer used.

The studies come from all over the world. Only two were carried out in the community (Chong-Neto 2005; Morrone 1990); six trials have been conducted in an inpatient setting (Ba 1989; Burrows 2004; Coker 1995; Dewar 1999; Morley 1988; Parkin 1995), and all others were conducted in hospital emergency departments (although Direkwatanachai 2008 also recruited children from outpatients, and Yasmin 2012 only reports that the trial was carried out in the Department of Paediatrics). The single pre-hospital study comparing nebulisation to metered-dose inhaler (MDI) (Campbell 1995) was excluded, as there was no randomisation. Different beta^2 -agonists, spacers and nebulisers were represented in the studies.

The dosage ratio between delivery methods varied from 1:1 to 1:13, with the larger doses administered via nebuliser. The median dose administered via nebuliser was four times that administered via spacer, a dosage ratio of 1:4 (interquartile range (IQR) 1:2 to 1:8).

Many recent studies used multiple treatments at 10- to 30-minute intervals (Batra 1997; Chong-Neto 2005; Chou 1995; Colacone 1993; Direkwatanachai 2008; Duarte 2002; Idris 1993; Jamalvi 2006; Leversha 2000; Ploin 2000; Rao 2002; Rodrigo 1993; Rodrigo 1998; Sannier 2007; Valencia 1999; Vivek 2003; Yasmin 2012). Most studies used commercially-available spacers (Aerochamber, Babyhaler, InspirEase, Lite Aire, Nebuhaler and Volumatic), but two studies from Brazil and one from Bangladesh (Chong-Neto 2005; Duarte 2002; Yasmin 2012) used home-made spacers in the form of a 500 mL mineral water plastic bottle. Duarte 2002 coated the bottle with detergent to avoid electrostatic charge, whilst Chong-Neto 2005 included 10 children treated with aerochamber and 10 children using a 500 mL water bottle glued onto the MDI with Araldite. The studies using salbutamol all used the racemic form of the drug.

Excluded studies

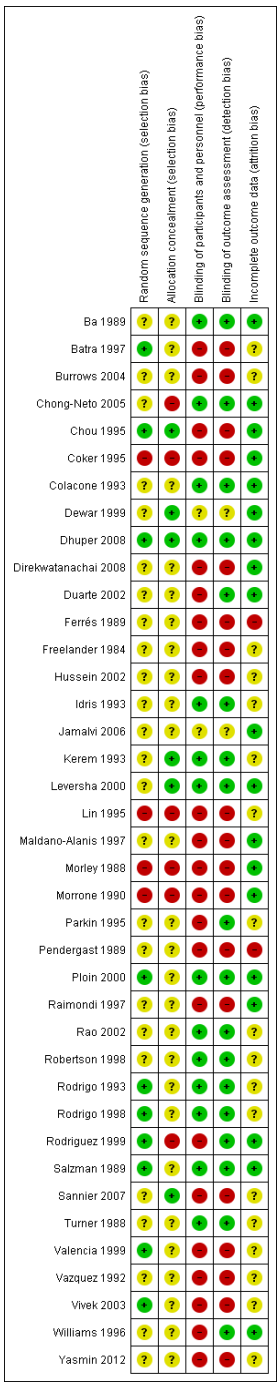
See Characteristics of excluded studies tables for full details.

Risk of bias in included studies

Overall, the methodological quality of the included studies was variable, with sequence generation and allocation concealment not described in many studies (see Characteristics of included studies). Many studies did not comment on withdrawals and dropouts, and also did not report whether intention-to-treat analysis was employed, but in short-term trials of acute treatment we would not expect large numbers of dropouts. The hospital admission rate reported in one study has been amended using an intention-to-treat analysis (Colacone 1993).

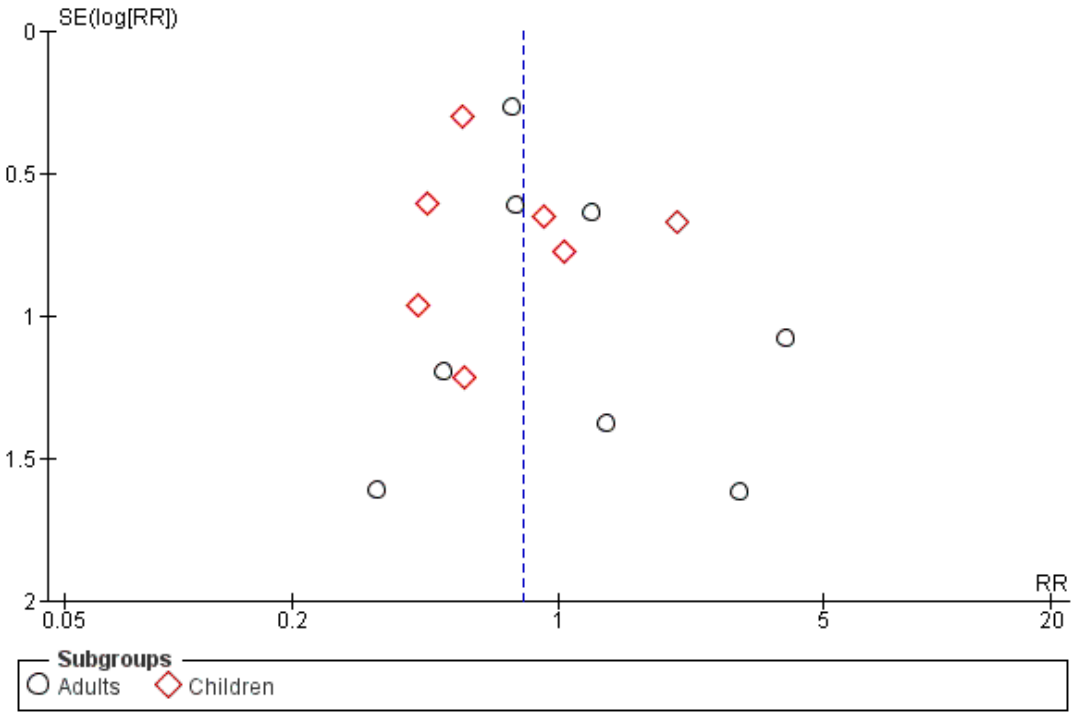
In general the sample size of many individual studies was small, (range 18 to 196 participants in the emergency-room studies, and 28 to 61 for inpatients). Whilst eight of the 13 studies in adults used a double-blind, double-dummy design (Colacone 1993; Dhuper 2008; Idris 1993; Rodrigo 1993; Rodrigo 1998; Rao 2002; Salzman 1989; Turner 1988) only six of the 26 studies in children were double-blind (Ba 1989; Chong-Neto 2005; Kerem 1993; Leversha 2000; Ploin 2000; Robertson 1998); see Figure 2.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



A funnel plot of hospital admissions did not suggest publication bias in relation to the primary outcome of this review, since the smaller studies showed equal spread of results on both sides of the overall risk ratio (Figure 3).

Figure 3. Funnel plot of comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), outcome: 1.1 Hospital admission.



'Summary of findings' Tables

The assessments of risks of bias have been incorporated in two 'Summary of findings' tables, which are presented separately for children (Summary of findings for the main comparison) and adults (Summary of findings 2) for the 2013 update of this review.

Effects of interventions

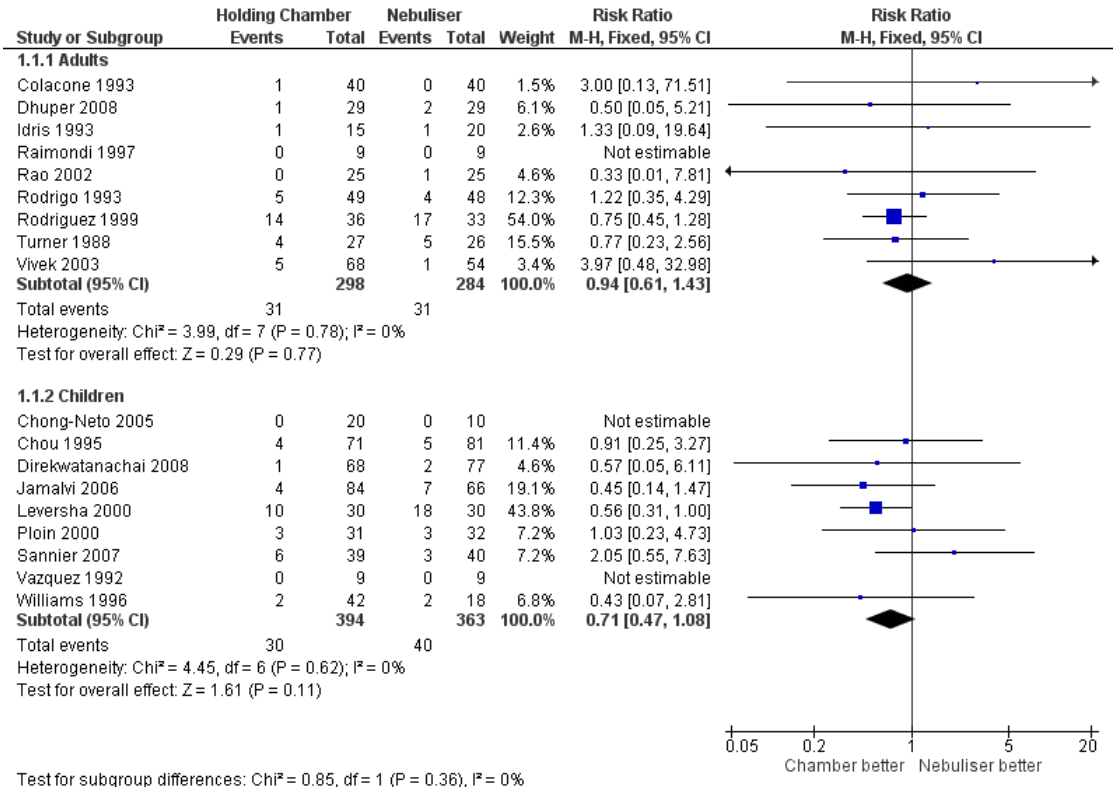
See: **Summary of findings for the main comparison** Multiple treatment of beta$_2$ -agonist via spacer (chamber) compared to nebuliser for children with acute asthma; **Summary of findings 2** Multiple treatment of beta$_2$ -agonist via spacer (chamber) compared to nebuliser for adults with acute asthma

Spacer versus nebuliser multiple treatments

Primary outcome: Hospital admission

Hospital admission rates did not differ significantly on the basis of delivery method in adults (risk ratio (RR) 0.94; 95% confidence interval (CI) 0.61 to 1.43, 9 trials, n = 582; Analysis 1.1) or in children (RR 0.71; 95% CI 0.47 to 1.08, 9 trials, n = 757; Figure 4). No significant heterogeneity was observed.

Figure 4. Forest plot of comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), outcome: 1.1 Hospital admission.



Subgroup analysis by type of spacer

In the light of the decision to temporarily withdraw Volumatic spacers from the UK market in 2005, we carried out a post hoc sensitivity analysis according to whether Volumatic spacers were used in each study. The type of spacer used is documented in Table 1 and this shows that the majority of adults and children studied used other types of spacer. No significant differences were found between the results from trials using Volumatic (166 adults and 163 children) and those using other types of spacer (366 adults and 515 children). There were no significant differences between the results for Volumatic and other spacer types in either adults or children (see Analysis 4.1). No studies included a direct comparison between Volumatic and other types of spacer.

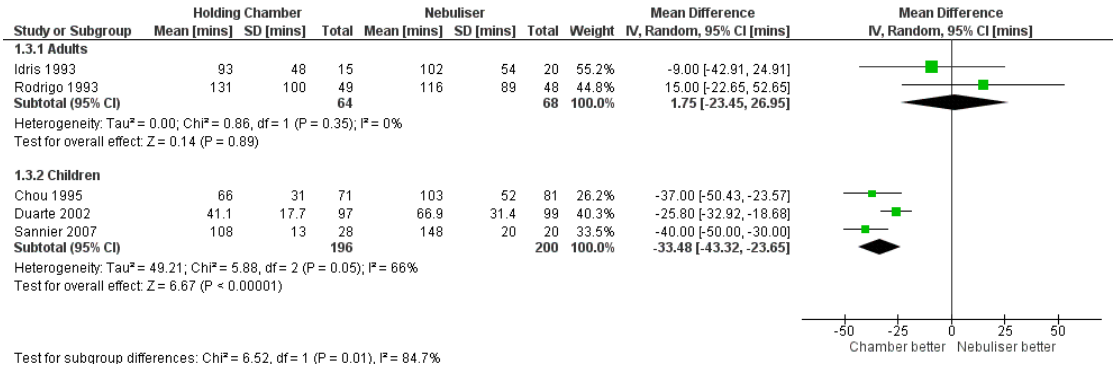
Secondary outcome: Treatment failure

Three studies in children did not report admissions but did report data on poor outcomes (Batra 1997; Leversha 2000; Yasmin 2012). When these are pooled together with the data on hospital admissions, the risk ratio in children of admission or poor outcome is not significantly different between spacer and nebuliser (RR 1.00; 95% CI 0.75 to 1.33, 12 trials, n = 937; Analysis 1.2). The definition of treatment failure varied across studies, and we included these data post hoc.

Secondary outcome: Time spent in emergency department

Time spent in the emergency department (ED) showed significant heterogeneity when the results from adults and children were pooled in the original version of this review, (Chi^2 = 8.2, df = 2, P < 0.02). However, no significant heterogeneity was demonstrated when adults and children were analysed separately at that time. The results for adults and children have therefore been shown in separate subgroups in the analyses in Figure 5.

Figure 5. Forest plot of comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), outcome: 1.3 Duration in emergency department (minutes). [mins].



Duration in the ED in children was significantly shorter with the spacer (mean difference (MD) -33 minutes; 95% CI -43 to -24 minutes, I^2 = 66%, 3 studies, n = 398; Analysis 1.3). This finding is based on three studies (Chou 1995; Duarte 2002; Sannier 2007), containing 396 participants, in which the median duration in ED on nebulised treatment was 103 minutes. The studies in children were open-label and did not use a double-dummy design, whereas the studies in adults were double-dummy so adults would have received both nebuliser and spacer. This is likely to have had a bearing on these results as nebulisation is much more time-consuming than use of MDI and spacer (Duarte 2002). In adults the duration of the ED visit was similar in both groups (MD 2 minutes; 95% CI -23 to 27 minutes; Analysis 1.2). Results in children and adults are shown using a random-effects model.

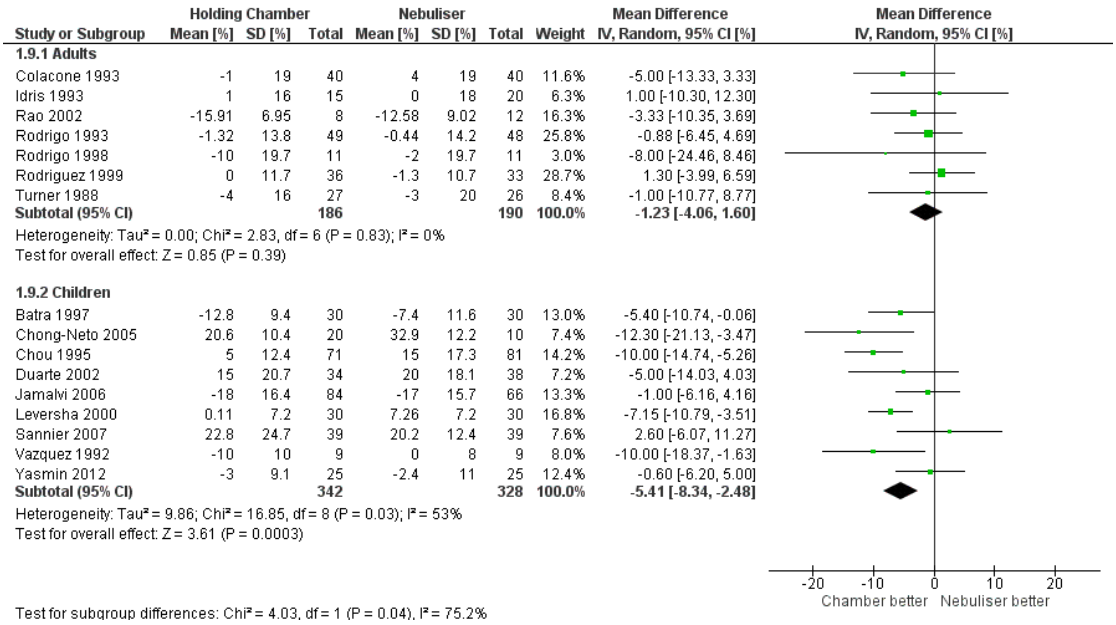
Secondary outcome: Lung function

No significant differences were demonstrated between the two delivery methods in terms of peak flow and forced expiratory volume (FEV_1) at 30 minutes and at the end of the study in either adults or children. More specifically, in the four studies in adults that included analysis of changes in lung function in the most severely affected participants (e.g. FEV_1 < 30% predicted), there was no statistically significant difference between the two delivery methods (MD -1.6% predicted; 95% CI -7.69 to 4.49%). The only study (Maldano-Alanis 1997) which found a significant difference in FEV_1 between the nebuliser and spacer groups used a low dose of salbutamol via the spacer (200 mcg), and showed a significant decline in FEV_1 in this group three to six hours after the treatment was administered. This trial could not be included in the analysis as no standard deviations were reported and the authors did not respond to requests for further information. Maldano-Alanis 1997 did not contribute to the primary outcome of hospital admission.

Secondary outcome: Pulse rate

Pulse rate after treatment (expressed as % change from baseline), was significantly lower when a spacer was used in children (MD -5.41 %; 95% CI -8.34 to -2.48, I^2 = 53%, random-effects). In adults, no significant difference was found between methods (MD -1.23 %; 95% CI -4.06 to 1.60, random-effects). These results were similar for fixed- and random-effects models. There was a significant difference between the pulse changes in adults and children (test for subgroup differences: Chi^2 = 4.03, df = 1 (P = 0.04), I^2 = 75.2%, random-effects, see Figure 6).

Figure 6. Forest plot of comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), outcome: 1.9 Rise in pulse rate (% baseline) [%].



Secondary outcome: Oxygen saturation

There were no data available in adults for the outcome oxygen saturation. Oxygen saturation in children was not significantly different between groups at the end of the studies (MD -0.19%; 95% CI -0.61% to 0.24%, 6 studies, 476 children; Analysis 1.10). One study (Duarte 2002), however, reported that 25% of children treated with oxygen-driven nebuliser suffered desaturation at some point during treatment compared to 9% of those treated with MDI and spacer (P = 0.006).

Secondary outcome: Adverse events (tremor)

Development of tremor was more common with nebuliser treatment in the four studies that reported this in children (RR 0.64; 95% CI 0.44 to 0.95, random-effects), but the test for interaction between adults and children was not significant.

Other secondary outcomes

No significant differences were demonstrated between the two delivery methods for the other measured outcomes: change in respiratory rate and the number of participants given steroids.

We have made no attempt to combine the findings for symptom score as the scales used were highly variable and the standard deviation of results were rarely reported.

Spacer versus nebuliser single treatments

We did not pool results from single-treatment studies because of concern over confounding by the variable amounts of beta^2 -agonists delivered to the airways from the different delivery methods. Blood gas results were reported in two studies (Kerem 1993; Lin 1995). The participant numbers were small but both show less deterioration in gases with a spacer. One study (Lin 1995) also measured lung function 15 minutes after the start of treatment and found a significantly greater rise in peak expiratory flow (PEF) at this time with the spacer (MD 10.1% predicted; 95% CI 15.7 to 4.4%); this study is of low methodological quality, so this information should be interpreted with caution. More recently, Hussein 2002 reported similar changes in oxygen saturation in a single-treatment study in 60 children. The author has not responded to a request for further details.

Spacer versus nebuliser Inpatient studies

Individual patient data have been provided by the authors of Burrows 2004 on children who were aged two years or more and these have been incorporated into the 2013 update.

Primary outcome: Duration of hospital admission

The primary outcome of duration of admission was available from four studies (Burrows 2004; Dewar 1999; Morley 1988; Parkin 1995) but the results in Dewar 1999 were skewed and presented as medians so are not suitable for combination with the other two studies in children. The duration of admission did not show a significant difference between delivery methods in a single study in adults (MD -0.60 days; 95% CI -3.23 to 2.03) or in the two studies in children (MD 0.33 days; 95% CI -0.10 to 0.76), see Analysis 3.1.

Secondary outcomes: Respiratory rate, heart rate and oxygen saturation

It was possible to combine the data provided by Burrows 2004 with the results from Dewar 1999 for three of the secondary outcomes (including 76 children).

There were no significant differences found in these children between spacers and nebulisers in respiratory rate (MD -0.91; 95% CI -3.20 to 1.38, Analysis 3.9), heart rate (MD 1.06; 95% CI -5.48 to 7.61, Analysis 3.10) or oxygen saturation at discharge (MD 0.12; 95% CI -0.42 to 0.66, Analysis 3.11).

The results from the individual studies have been outlined below.

Ba 1989 was a single-dose comparison in children, and did not measure the primary outcome (time to discharge). The design was double-blind with double dummy. Continuous intravenous aminophylline was given to all children in both groups. There was a significant difference between groups in baseline lung function, spacer baseline FEV_1 38.2 (SD 7.9)% predicted and nebuliser 49.8 (SD 14)% predicted. Results are only presented as change from baseline, and this will favour the spacer group. There was no significant difference in FEV_1 between groups over three hours, and the significant advantage for the spacer in change in forced vital capacity (FVC) is probably due to baseline difference. The paper reported significantly more children treated with spacer increased their pulse rate at 10 minutes compared to the nebuliser group, but this data could not be used as the number of participants with increased pulse reported in the spacer group (17) was greater than the group total (14).

Coker 1995 was a single-dose comparison in children, and did not measure the primary outcome (time to discharge). There was no blinding and participants were allocated by alternation. No co-interventions were reported and no significant differences in respiratory score or PEF were found between groups over six hours.

Dewar 1999 compared multiple treatments in children, given up to one-hourly by each delivery method. Allocation was concealed with sequential pre-sealed envelopes and all children received oral steroids on admission and repeated on subsequent mornings for three to five days according to their recovery. No blinding was reported. Data for duration of stay were noted to be skewed by small numbers of lengthy inpatient stays so medians were used which did not show a significant difference between groups, (36.5 hours for the spacer group and 40 hours for the nebuliser group). Although readmission rates were lower in the spacer group, this group were also given a written asthma plan and this may have confounded the results for readmission and symptoms after discharge. Children requiring immediate intravenous treatment were excluded from the study, and five children were withdrawn due to deterioration requiring intravenous treatment (three in the spacer group and two in the nebuliser group). The authors calculated a significant cost benefit for the spacer group in terms of drug costs, GBP 5.43 per participant in the spacer group and GBP 20.25 in the nebuliser group ($P < 0.001$).

Morley 1988 was the only inpatient study in adults, and used multiple treatments. Allocation was by alternation and no blinding was described. Intravenous aminophylline and methylprednisolone were given at standard doses. Mean duration of hospitalisation was not significantly different between groups, 5.8 days in the spacer group and 6.4 days in the nebuliser group, mean difference of -0.6 days (95% CI -3.2 to 2.0). No significant differences were found in lung function between groups.

Parkin 1995 compared multiple treatments in younger children (aged one to five years), but gave both salbutamol and ipratropium by spacer or nebuliser. The research nurse only was blinded and all children received intravenous or oral steroids. There was no significant difference in hours to discharge (spacer 53 hours and nebuliser 46 hours), hours to the change of treatments to four-hourly intervals or total number of inhaled doses received. Nine participants in the spacer group crossed over to nebuliser treatment, but their results were analysed by original group assignment (intention-to-treat analysis).

Burrows 2004 studied 29 children aged one to six years old with moderate to severe asthma according to British Thoracic Society (BTS) guidelines, who were hospitalised between September 2003 and February 2004. No significant differences were reported in any outcomes except for cost (which was GBP 7.68 per participant in the nebuliser group and GBP 5.96 per participant in the spacer group). The length of stay was 16.5 hours in the nebuliser group and 26.5 hours in the MDI and spacer group, with change in respiratory rate of -5.4 and -6.3, change in pulse of 2.9 and 4.6, and change in oxygen saturation of 0.53 and 1.07 for nebuliser and spacer, respectively. The authors of Burrows 2004 have provided individual patient data for the children aged 2 years or more from this study and this has been added to duration of hospital admission from Parkin 1995. There was no significant difference in duration of admission (MD 0.33 days; 95% CI -0.10 to 0.76) and shown in Analysis 3.1. Similarly the individual patient data from this study have been combined with results from Dewar 1999 as outlined in the secondary outcomes above.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Multiple treatment of beta$_2$ -agonist via spacer (chamber) compared to nebuliser for adults with acute asthma

Patient or population: Adults with acute asthma
Settings: Community or Emergency Department
Intervention: Multiple treatments with beta$_2$ -agonist via spacer (chamber)
Comparison: Multiple treatments with beta$_2$ -agonist via nebuliser

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Nebuliser	Multiple treatment of beta$_2$-agonist via spacer (chamber)				
Hospital admission	**109 per 1000**	**103 per 1000** (67 to 156)	**RR 0.94** (0.61 to 1.43)	582 (9 studies)	⊕⊕⊕◯ **moderate**[1,2]	
Duration in emergency department (minutes).	The mean duration in emergency department (minutes) in the control groups was **109 minutes**	The mean duration in emergency department (minutes) in the intervention groups was **2 minutes longer** (23 minutes shorter to 27 longer)		132 (2 studies)	⊕⊕⊕◯ **moderate**[2]	
Final rise in FEV$_1$ (% predicted)	The mean final rise in FEV$_1$ (% predicted) in the control groups was **22 % predicted FEV$_1$**	The mean final rise in FEV1 (% predicted) in the intervention groups was **0.96% higher** (2.54 lower to 4.46 higher)		307 (6 studies)	⊕⊕⊕⊕ **high**[3,4]	

Rise in pulse rate (% baseline)	The mean rise in pulse rate (% baseline) in the control groups was **-2% of baseline**	The mean rise in pulse rate (% baseline) in the intervention groups was **1.23 lower** (4.06 lower to 1.6 higher)		376 (7 studies)	⊕⊕⊕⊕ **high**[3,4]
Number of participants developing tremor	**185 per 1000**	**207 per 1000** (122 to 351)	**RR 1.12** (0.66 to 1.9)	234 (4 studies)	⊕⊕⊕◯ **moderate**[2,3]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Mostly double-blind studies.
[2] Confidence intervals too wide to assess whether either treatment is better.
[3] All double-blind studies.
[4] Very small absolute differences.

DISCUSSION

Summary of main results

Overall, we found no significant advantage of wet nebuliser over metered-dose inhaler (MDI) with spacer administration of beta^2 -agonists in the treatment of acute asthma when treatments are repeated and titrated to the response of the participant for our primary outcome of hospital admissions. Thus the major take-home message from this review is that nebulisers have not been shown to be superior to spacers in preventing hospital admissions. Importantly we found that children had shorter emergency department (ED) visits when short-acting beta^2 -agonists were administered via spacer rather than nebuliser. The entire confidence interval indicated a patient-important benefit - we think parents would be happy to spend between 23 to 43 minutes less in the ED if their child was having an asthma attack, potentially saving health services time and money. It is not possible to say whether there is a time benefit in adults; this may be partly because all the adult trials contributing to this outcome were double-blind and double-dummy. Since both groups received both nebuliser and spacer this may have confounded any possible time saving from using the spacer. In addition hypoxia was reduced, and pulse rates and risk of tremor were lowered compared to participants receiving the same beta^2 -agonist via wet nebulisation.

In clinical practice the dose of beta^2 -agonist delivered to the airways varies depending on the type of nebuliser or spacer used and the characteristics of the individual's airways at that time (Lipworth 1997). Uncertainty over the dose of beta^2 -agonists required through any delivery method was overcome in many of the studies (613 adults and 1203 children) by repeating treatments at short intervals. For example, one respule (via nebuliser) or four to six puffs (via spacer) every 10 to 30 minutes until the person responded to treatment (see Table 1 for a list of trials using multiple treatments). This approach reduced confounding by different dosages of drug delivered.

Overall completeness and applicability of evidence

People with life-threatening asthma exacerbations were excluded from the studies (for example those who were considered for ventilation). We do not know how this patient group would respond to treatment using spacers, or indeed whether they would be able to use a spacer under these circumstances.

Only two small studies were carried out in a community setting (Chong-Neto 2005; Morrone 1990) and this review did not compare people being randomised to receive either nebuliser or spacer at home for delivery of beta^2 -agonists when their symptoms get worse. While we do not have evidence in these populations, it is logical to conclude that provided people are proficient at using their spacer (or can clearly instruct their child to use their spacer correctly) there is no advantage in buying an expensive home nebuliser when a spacer is cheaper and more portable. However, our confidence in this statement is low as the evidence in this review comes form an ED setting where treatment can be supervised by health professionals.

Few authors reported specifically on numbers of people presenting who were excluded from each study, and intention-to-treat analysis was not usually reported. Thus it is not entirely clear how these results apply to all people who present with an exacerbation.

Analysis of the data regarding lung function tests in many papers was complicated by a lack of standardised reporting. In addition, data regarding standard deviation related to the changes that were measured were not always reported. Peak flow and forced expiratory volume (FEV_1) were the most commonly reported measurements and these were both included in the outcome tables. These concerns are not enough to overturn our confidence in the patient-important outcome of reduced time in the ED in children.

Quality of the evidence

Sequence generation and allocation concealment were unclear in many of the included studies, and only eight studies in adults and six studies in children used a double-bind (double-dummy) design (see Figure 2). Performance and assessment bias might therefore have reduced the size of true differences between the two delivery methods.

Agreements and disagreements with other studies or reviews

Use of oral or parenteral steroids

Successful response to beta^2 -agonists does not diminish the necessity to consider oral steroids in acute attacks of asthma. A previous meta-analysis demonstrated that steroids clearly reduce relapses when given to patients following discharge, and reduce hospitalisation when used early in the course of emergency treatment (Rowe 2007).

Dosage of beta^2 agonist

The studies included in this review used nominal dosage ratios between nebuliser and spacer that varied from 1:1 to 1:13 (lower dose in the spacer). One of the included studies plotted a log dose-

response curve (Colacone 1993); the equivalent dose ratio found in this study was 1:6 with the lower dose in the spacer. In adults, no additional benefit was found using six puffs of salbutamol (100 mcg each) given at 10-minute intervals through a Volumatic spacer, when compared with four puffs at 10-minute intervals (Rodrigo 1996). A comparison in children between doses of 0.5 mg/kg and 1.5 mg/kg given at 20-minute intervals via nebuliser showed significantly greater improvement in lung function at the higher dose (Schuh 1989).

Experimental evidence suggests that the beta^2 -agonist should be released (actuated) into the spacer in individual puffs that can be inhaled by tidal breathing or single breaths (Gleeson 1988; Newman 1984). Some of the early studies mentioned difficulty with the valve movement with some spacers; however, this did not appear to be a problem in more recent studies. Some children may co-operate more with either spacer or nebuliser, so this may be an important factor in the choice of delivery method.

Type of spacer

Two studies compared different types of spacer; Chong-Neto 2005 studied 10 children with aerochamber and 10 with a home-made spacer constructed from a 500 mL mineral water bottle. The study failed to identify differences between the types of spacer other than lower pulse rates with the Aerochamber than with the home-made spacer. Williams 1996 included 20 children treated with an Aerochamber and 22 children treated with an ACE spacer (both around 150 mL) and found no significant differences between the groups in respiratory rate and lung function.

Overall comparisons between types of spacer are confounded by all the other differences between the designs of each trial. In view of the discontinuation of Volumatic spacers in the UK in 2005, additional details to allow identification of type of spacer used have been added in Table 1. This indicates that the findings of this review for the primary outcome of hospital admission are unchanged in children when trials using Volumatic spacers are excluded, but the confidence intervals widen for adults as fewer data contribute to the outcome. We found no significant subgroup differences for any outcome between the trials using Volumatic or other spacers.

Cost of treatment

Cost considerations may dictate which delivery system is used in different settings. In many parts of the world nebulisation is not available in peripheral hospitals and clinics for economic reasons (Rao 2002). Several recent studies have now included a calculation of costs of drug treatment (Burrows 2004; Chong-Neto 2005; Dewar 1999; Dhuper 2008; Duarte 2002) and found a cost advantage for spacer delivery.

Total costs in a hospital setting are more complex to calculate; however, when patients return to the community the cost of a home nebuliser and respules is considerably more than an MDI and spacer (and the nebuliser requires regular maintenance). A before-after ED study (Newman 2002) assessed the consequences of changing the acute asthma treatment algorithm from nebulised to MDI/spacer albuterol (salbutamol). Admission rates did not rise following the change in delivery method and duration of stay in the ED fell significantly from 175 minutes to 164 minutes. There were also reductions in charges that did not reach significance. Lower relapse rates following the change to MDI/spacer delivery were confounded by other changes, such as an asthma bag containing a spacer, peak-flow meter, instructional handout and canister of inhaled corticosteroid given to the patients at discharge. This makes data on relapse rates difficult to interpret, although significant reductions were seen following the combined interventions. As expected, the total dose of albuterol given to patients was lower with MDI/spacer delivery.

Changing Practice

Current guidelines recommend MDI/spacer delivery of beta^2 -agonists in acute asthma (BTS/SIGN 2011; GINA 2012). However, implementing research findings is not an easy process, and Powell 2001 found that successfully changing hospital practice from nebulisers to spacers required a structured strategy to overcome the 'nebuliser culture' both in hospital medical and nursing staff, as well as parents and families of children with asthma. Osmond 2007 carried out a survey of the use of nebulisers and spacers in Canadian paediatric EDs, and found that 21% of emergency physicians used MDI and spacer; the largest perceived barriers amongst non-users included safety and costs, and the lack of a physician champion for change.

AUTHORS' CONCLUSIONS

Implications for practice

1. For adults seen and assessed for acute asthma, this review found no significant differences between the two delivery methods. Consequently, the choice of delivery method should reflect patient preference, practice situations and formal economic evaluation

2. In children, no outcomes were significantly worse with the spacers, and the available evidence suggests that in most cases nebulisers could be replaced with spacers to deliver beta^2 -agonists in acute asthma. Moreover, other observed benefits (time spent in emergency department, oxygenation and side

effects) may favour the groups treated with metered-dose inhaler (MDI) and spacer.

3. The experimental method adopted in many of the studies was to give repeated treatments at short intervals (e.g. one respule via a nebuliser or four puffs of a MDI via a spacer every 10 to 15 minutes). The number of treatments required was adjusted to the individual patient's response, overcoming the uncertainty of dosage delivery from different devices. Tidal breathing is easier for adults and children using a spacer for acute asthma, but each puff should be inhaled from the spacer before the next puff is delivered into the spacer. Current evidence is therefore based upon titrated treatment regimens and this should be considered when implementing any change in practice.

4. The studies excluded people with life-threatening asthma; therefore, the results of this meta-analysis should not be extrapolated to this patient population.

Implications for research

1. Further studies are required to confirm whether these findings, largely from hospital emergency departments, can be replicated in the community setting.

2. Further studies in children and adults with more severe asthma are required to confirm whether spacers are as efficacious as nebulisers in this group.

3. In order to avoid confounding due to differences in the dose of drug delivered to the airways, future studies should use multiple treatments at short intervals titrated against individual patient response.

4. Implementation of change to continue to overcome the 'nebuliser culture' needs further work.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ba 1989

Methods	Baseline characteristics: Comparable but the Chamber group had significantly lower FEV_1 at baseline ($P < 0.02$). Intention-to-treat analysis: not used.
Participants	Setting: Hospital inpatients, Canada. 27 children aged 7 - 18 years old (average age 11.9). Inclusion/exclusion criteria: Salbutamol nebulisers and IV aminophylline given on admission. 3 hours post- if FVC and FEV_1 were still < 65% predicted value then included, if above excluded
Interventions	$Beta_2$ -agonist: Salbutamol. Spacer: Nebuhaler 750 mL pear-shaped. Nebuliser: Hudson, up-draft 11 nebu-mist. Driven by continuous flow oxygen output 6L/min. Chamber Group: 2 mL 0.9% saline (placebo) via nebuliser, immediately followed by continuous tidal breathing of 2 puffs salbutamol every 10 seconds (total 12 puffs = 1.2 mg) with MDI + Nebuhaler. Nebuliser Group: 1 mL (5 mg) salbutamol added to 1 mL of 0.9% saline, immediately followed by tidal breathing with a placebo via MDI + Nebuhaler. Dose ratio 1:4 Co-interventions: All children had continuous IV aminophylline
Outcomes	FEV_1 and FVC, pulse, blood pressure, respiratory rate, side effects. Assessed at -11 mins (before) and 10, 30, 60, 90, 120, 180 (after) inhalation from the MDI and spacer. Maximum change in FEV_1 and FVC from baseline
Notes	Lower baseline FEV_1 in the spacer group may have contributed to the larger improvement from baseline in this group

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details.
Allocation concealment (selection bias)	Unclear risk	"subjects were entered in a double-blind randomised manner".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.

Ba 1989 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	"All patients completed the study". No withdrawals

Batra 1997

Methods	Baseline characteristics: comparable. Power analysis: 30 in each group designed to detect a 30% difference in response rate
Participants	Setting: India. Emergency Department. 60 children aged 1 - 12 years (average age 4 years). PEF at presentation was under 40% predicted in the 16 children able to undergo this evaluation. Inclusion criteria: over 2 previous attacks of wheezing in response to allergens and exercise as well as infection. Exclusion criteria: TB, heart, liver, kidney or lung disease. Skeletal disorders
Interventions	Beta$_2$ -agonist: Salbutamol. Spacer: Volumatic (M/s Cipla) 750 mL. Dosage: 2 puffs (200 mcg) given every 5 to 10 minutes for 60 minutes. Nebuliser: no details. Dosage: 0.15 mg/kg in 2.5 mL saline given 3 times at 20-minute intervals. Co-interventions: all given humidified oxygen and none were given steroids
Outcomes	Further treatment (?admission), PEF in 16 children, blood gases, symptoms score
Notes	This trial was included as the mean age of the children was over 2 years old. No response from authors to requests for further details

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.

Batra 1997 (*Continued*)

Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No mention of withdrawals.

Burrows 2004

Methods	Baseline characteristics: not available Intention-to-treat analysis: not available.
Participants	Southampton General Hospital, UK. 29 children aged 1 - 6 years admitted to hospital with moderate or severe asthma. Inclusion criteria: moderate or severe asthma according to BTS criteria. Exclusion criteria: details not available.
Interventions	Beta$_2$ -agonist: Salbutamol. Spacer: Volumatic (up to 10 puffs given). Nebuliser: details not available, but dose of 2.5 to 5 mg given at the discretion of the admitting physician. Co-interventions: details not available.
Outcomes	Duration of admission to hospital, oxygen saturation, increase in heart rate, increase in respiratory rate, drug costs
Notes	No SD data provided in abstract. Details for children over 2 years of age provided by the author

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available.
Allocation concealment (selection bias)	Unclear risk	Infomation not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	Data provided on 25 out of 29 children

Chong-Neto 2005

Methods	Baseline characteristics: comparable. Power calculation:carried out on the basis of a 15% difference in FEV_1 between groups
Participants	Critiba, Brazil. 24-hour emergency health unit. 40 children aged 6 - 18 years old. 30 of these were included in this review (10 in each arm as detailed below). Inclusion criteria: Acute asthma attacks. Children were able to use the devices and carry out lung function testing. Exclusion criteria: History of cardiac and pulmonary diseases other than asthma, clinical score < 3, forced expiratory flow in the first second (FEV_1) less than 20% and greater than 80% of the predicted value. Smokers (> 10 packs of cigarettes/year), and children treated with short-acting and long-acting $beta_2$-agonists in the last 24 hours, corticosteroids on the last 7 days, and also those receiving xanthines, were also excluded
Interventions	$Beta_2$-agonist: Salbutamol (Albuterol). Spacer A: Aerochamber, 4 x 100 mcg separate actuations of salbutamol given at 30-second intervals, inhaled using single deep breath per actuation. This was given 3 times at 20-minute intervals. Home-made Spacer: 500 mL plastic water bottle, 4 x 100 mcg separate actuations of salbutamol given at 30 second intervals, inhaled using single deep breath per actuation. This was given 3 times at 20-minute intervals. Nebuliser: Pari Jet, 0.15 mg/kg salbutamol given every 20 minutes in 3 mL saline driven by Proned ultra compressor (air driven). Dosage ratio: spacer:nebuliser = 1:12.5. Co-interventions: not specified. (The further 10 children treated with dry powder inhaler were not included in this review)
Outcomes	FEV_1, admission to hospital, change in symptom score, increase in heart rate, tremor, nausea, vomiting, hypokalaemia. Full data provided by authors
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; drawing of lots used but unclear how numbered lots were drawn up
Allocation concealment (selection bias)	High risk	Children randomised themselves by drawing lots.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.

Chong-Neto 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	All participants completed the study

Chou 1995

Methods	Baseline characteristics: comparable. Intention to treat analysis: not required.
Participants	New York. Urban paediatric Emergency Department. 152 children aged 2 years or older. Mean PEF at presentation 56% and 53% in the treatment and control group. Inclusion criteria: current wheeze and history of at least 2 episodes of wheezing. Exclusion criteria: no participants were excluded from the study, but exclusion criteria included chronic illness, presenting oxygen saturation less than 90% or symptom score >12
Interventions	Beta$_2$ -agonist: Salbutamol (Albuterol). Spacer: Aerochamber, 3 x 90 mcg actuations of salbutamol given every 20 minutes, inhaled using 5 normal breaths per actuation. (Mean 2.3 treatments given). Nebuliser: Acorn II, 0.15 mg/kg salbutamol given every 20 minutes in 3 mL saline driven by oxygen at 6 L per minute (Mean 2.5 treatments given). Co-interventions: oxygen was given to all participants with an oxygen saturation of less than 94% while breathing room air. Administration of steroids and other medication was at the discretion of the treating physician
Outcomes	Admission to hospital, duration in emergency department, change in symptom score, final Peak Flow (in children old enough to perform test), oxygen saturation, increase in heart rate, administration of steroids
Notes	Standard deviation of results and details of randomisation obtained from author; SD of change in lung function estimated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.

Chou 1995 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	All participants completed the study.

Coker 1995

Methods	Baseline characteristics: Comparable. Intention-to-treat analysis: Not used.
Participants	Setting: Hospital inpatients, Turkey. 36 children, 12 in each group; 2 groups considered. Mean age 10.33 (SD 1.15) (chamber), 11.75 (SD 1.60) (nebuliser). Inclusion Criteria: Children over 9 years, admitted with acute asthma crisis. Exclusion criteria: if received any medicine in the last 8 hours
Interventions	Beta$_2$ -agonist: Salbutamol Spacer: 750 mL Volumatic spacer using tidal breathing. 200 mcg (given twice with interval of 2 minutes in between). Nebuliser: Pari-inhaler boy (ultrasonic) nebuliser driven by compressed air. 0.05 - 0.1 mg/kg (max dose of 2.5 mg) nebules. Co-interventions: none.
Outcomes	Respiratory score (nasal flaring, cyanosis, retractions, wheezing), PEFR, respiratory rate, heart rate, blood pressure. All measured at 5, 15, 30, 240, and 360 (6 hours) minutes after treatment
Notes	Confirmation of doses, gained from author as well as method of randomisation (alternation), withdrawals and dropouts and co-interventions. 3rd arm of this trial using MDI only was disregarded.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Alternate allocation.
Allocation concealment (selection bias)	High risk	Allocation by alternation at high risk of bias in terms of concealment of allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.

Coker 1995 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	No withdrawals or dropouts reported in correspondence with the authors

Colacone 1993

Methods	Baseline characteristics: comparable. Intention-to-treat: not used in paper but carried out from data presented for hospital admissions Power calculation: performed, estimated 80%.
Participants	Setting: Canada. Hospital Emergency Department. 80 adults mean age 41 (SD 18) and 43 (SD 19) years. Mean FEV_1 (% predicted) at presentation: Spacer 55% (SD 15), nebuliser 54% (SD 18). Inclusion criteria: acute asthma, FEV_1 < 70% predicted, over 18 years old, able to perform spirometry. Exclusion criteria: pregnancy, complicating medical illness, already given nebulised or parenteral $beta_2$ -agonist in emergency department
Interventions	$Beta_2$ -agonist: Salbutamol (Albuterol). Spacer: Aerochamber. Dosage: 4 x 100 mcg puffs individually and inhaled by 1 slow inhalation at 1 minute intervals. Treatment given every 30 minutes until maximum bronchodilation achieved. Nebuliser: Disposable Updraft nebuliser. Dosage: 2.5 mg in 2 mL saline driven by oxygen at 5 to 8 L/min. Repeated every 30 minutes as above. Dosage ratio: spacer:nebuliser = 1:6. Co-interventions: steroids and aminophylline (stratified treatment arms)
Outcomes	Symptom score, FEV_1, heart rate, respiratory rate, presence of tremor
Notes	Cumulative dose-response curve showed a relative potency of 1:6 in favour of spacer. One participant was withdrawn from the spacer group due to clinical deterioration; included in review result as a hospital admission on intention-to-treat basis. Estimated SD for respiratory rate and pulse rate

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.

Colacone 1993 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	Full description of dropouts allowing ITT analysis of hospital admission data. One withdrawal from nebuliser group due to self-discharge and one from spacer group due to deterioration

Dewar 1999

Methods	8% did not complete follow-up post-discharge, but did complete trial in hospital. Baseline characteristics: comparable. Intention-to-treat: not used. Sample size: estimated from asthma admissions data from previous 2 years
Participants	Setting: Hospital inpatients, UK. 62 children aged 3 or above: mean age 6.9 years (chamber) 8 years (nebuliser). Inclusion criteria: over 3 years, admitted with acute asthma. Exclusion criteria: Children unable to use chamber mouthpiece effectively. Those requiring IV treatment. Those re-admitted during 5-month study period
Interventions	Beta$_2$ -agonist: Salbutamol. Spacer: Large volume spacer (Volumatic). Dosage: 100 mcg ,up to 10 puffs one-hourly. Children and parents in the spacer group were instructed and supervised on the optimal use of the delivery device. They were also provided with a written treatment plan for managing acute asthma. Nebuliser: jet nebuliser driven by oxygen 6 - 8 l/min. Dosage: 5 mg salbutamol up to 1-hourly. Co-interventions: All children received oral prednisolone at 2 mg/kg (max. dose 60 mg) on admission and repeated on subsequent mornings for 3 - 5 doses according to recovery. Oxygen was administered by face mask or nasal prongs in children who after bronchodilator treatment had Ox. saturations of < 93%
Outcomes	Hospital length of stay, cost, asthma morbidity 2 weeks after discharge, frequency of re-admissions during the study period and following 12 months
Notes	All families given same discharge advice re: management of acute attacks, but seems only chamber group received a written treatment plan. No response from author to confirm this. Participants lost to follow-up ignored: this can lead to bias

Dewar 1999 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other details available.
Allocation concealment (selection bias)	Low risk	Sequential presealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	3 withdrawals in spacer group and 2 in nebuliser group withdrawn due to deterioration. 11 participants excluded (2 immediately due to needing IV therapy, and 9 readmitted during trial and not re-studied.)

Dhuper 2008

Methods	Baseline characteristics: more women in the Lite Aire group. Intention-to-treat analysis: 2 withdrawn participants not included in the analysis. Power calculation: none.
Participants	Setting: New York. Emergency Department in 2 inner city hospitals in the Bronx. 58 adults aged 18 - 70 years. Median PEF at presentation: Spacer 220 L/min, Nebuliser 260 L/min. Inclusion criteria: acute asthma defined in NAEPP expert panel report II, as long as they could carry out PEF. Exclusion criteria: requiring intubation, more than 20 pack years of smoking, other co-existent systemic disease
Interventions	Beta$_2$ -agonist: Salbutamol. Spacer: Lite Aire 160 mL collapsible card dual chamber spacer (disposable). Dosage: 6 separate 90 mcg actuations inhaled by tidal breathing . Nebuliser: Cardinal Health Edison, NJ. Driving gas unclear. Dosage: 2.5 mg salbutamol. Each group had repeated treatment once an hour for up to 6 hours. Dosage Ratio: 1:8 (Spacer to Nebuliser). Co-interventions: Not specified. Placebo given to each group using the other delivery device

Dhuper 2008 (*Continued*)

Outcomes	Change in PEF, symptoms and hospital admission. Secondary outcomes included length of stay, cost and number of rescue treatments. Only hospital admission was used in this review as the other outcomes were not normally distributed and were not suitable for meta-analysis
Notes	Sponsored by Thayer Medical (who manufacturer Lite Aire spacer)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation table with block size of 4 used by pharmacist.
Allocation concealment (selection bias)	Low risk	All personnel involved in recruitment and medication delivery were blinded to randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	One withdrawal in each group (withdrawn consent and self discharge against medical advice). Fifteen participants excluded (5 did not fit inclusion criteria and 10 did not consent)

Direkwatanachai 2008

Methods	Baseline characteristics: Wood's asthma score below 4 in all group, no obvious baseline imbalance. Intention-to-treat analysis: all participants seem to be included in the analysis
Participants	Setting: 7 centres in Thailand. Emergency Departments and Outpatient clinics used. 68 children treated with MDI and spacer, 77 treated with nebuliser and 71 treated with Easyhaler (this arm was not used in the review) Mean ages 9.36 (+/- 2.68) years, 9.02 (+/- 2.57) in spacer and nebuliser groups. Median PEF at presentation: No details. Modified Wood's score: spacer 3.91 (1.22), nebuliser 3.57 (1.14). Maximum possible score is 7. Inclusion criteria: children attending ED or Outpatients with an asthma exacerbation (mild or moderate severity) Exclusion criteria: presence of other conditions, brittle asthma, severe exacerbation re-

	quiring intensive care or mechanical ventilation, allergy to salbutamol, repeated exacerbation within 7 days of entry into the study, or not able to use the DPI
Interventions	Beta$_2$ -agonist: Salbutamol. Spacer: Volumatic. Dosage: 6 x 100 mcg actuations (no details of separate actuations), repeated 3 times at 20-minute intervals. Nebuliser: No details. Driving gas oxygen or compressed air at 6 - 8 L/min. Dosage: 0.15 mg/kg salbutamol given up to maximum of 5 mg. Each group had repeated treatment up to 3 doses. Dosage Ratio: 1:8 for those given 5 mg via nebuliser (Spacer to Nebuliser). Co-interventions: None specified. Third arm of study using Easyhaler was not considered for this review
Outcomes	Primary outcome: Change in Wood's score. Secondary outcomes: Admission to hospital, asthma revisit within 3 days, use of systemic steroids, adverse events, oxygen saturation, increase in heart rate Missing data only reported for adverse event data, where 22 missing from spacer group and 29 from nebuliser group
Notes	No report of whether or not there were conflicts of interest, but Harn Thai Pharma provided all study medications and co-ordination of investigators meetings

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	No withdrawals. .

Duarte 2002

Methods	Baseline characteristics: no significant differences. Intention-to-treat analysis: not described. Power calculation based on 15 L/min difference in PEF.
Participants	Setting: Brazil. Emergency Room. 196 children aged 4 - 15 years. Mean PEF at presentation: Spacer 174 L/min, Nebuliser 173 L/min. Inclusion criteria: 2 or more previous acute exacerbations, mild to moderate current attack (PEF 50% to 79% of predicted). Exclusion criteria: severe acute asthma (PEF under 50% predicted), patients unable to perform PEF, or use delivery devices, patients who had used controller or rescue medication in the past 2 weeks, and patients with complications (pneumothorax, pneumonia)
Interventions	Beta$_2$ -agonist: Salbutamol. Spacer: 500 mL plastic mineral water bottle coated with detergent. Dosage: 5 separate 100 mcg actuations inhaled by tidal breathing for 20 seconds. Nebuliser: Nevoni (Sao Paulo, Brazil). Driving gas oxygen at 6L/min. Dosage: 0.15 mg/kg salbutamol given up to maximum of 5 mg Each group had repeated treatment up to 3 doses. Dosage Ratio: 1:4 - 10 (Spacer to Nebuliser). Co-interventions: Not specified.
Outcomes	PEF, Pulse oximetry, heart rate, respiratory rate, clinical score, duration in Emergency Room
Notes	Participants were discharged from the study when the PEF rose to 80% predicted or higher. SD given for absolute values imputed for changes in heart rate and respiratory rate. PEF data not shown as % predicted so not included

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	No withdrawals.

Ferrés 1989

Methods	Baseline characteristics: no details. Intention-to-treat analysis: withdrawn participants not included in the analysis
Participants	Setting: Barcelona, Spain. Emergency Department in a hospital. 100 children. Mean age 8.6 (+/- 2.8) years. Median PEF at presentation: No details. Inclusion criteria: children attending ED with an asthma exacerbation (no details of severity)
Interventions	Beta$_2$ -agonist: Salbutamol. Spacer: 750 mL spacer. Dosage: 25 puffs over 60 minutes . Nebuliser: No details. Dosage: 5 mg salbutamol (possibly as a single dose). Dosage Ratio: 1:2 (Spacer to Nebuliser). Co-interventions: Not specified.
Outcomes	PEF, pulse, respiratory rate, blood pressure and clinical score. Hospital admission data were obtained from correspondence with the author
Notes	Published in abstract only.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	High risk	Uneven missing date in each group reported in correspondence with authors. Nine withdrew from spacer group and two from nebuliser group. (41/50 evaluated for admission in spacer group and 48/50 in nebuliser group)

Freelander 1984

Methods	Baseline characteristics: comparable, but mean age 9.1 and 6.1 in treatment and control groups. Intention-to-treat analysis: none.
Participants	Setting: Australia. Accident and Emergency Department. 28 children aged 3 - 13 years. Mean PEF(% predicted) at presentation: spacer 55%, nebuliser 65%. Inclusion criteria: no details. Exclusion criteria: beta$_2$ -agonist in previous 2 hours.
Interventions	Beta$_2$ -agonist: Terbutaline. Spacer: Nebuhaler. Dosage: 5 puffs (1.25 mg) under 20 kg, 10 puffs (2.5 mg) over 20 kg. Details of inhalation technique not given. (single treatment). Nebuliser: Hudson driven by air at 6 L/minute. Dosage: 2.5 mg in 2 mL saline under 20 kg, 5 mg in 2 mL saline over 20 kg. (single treatment). Dosage Ratio: spacer:nebuliser = 1:2. Co-interventions: no details.
Outcomes	Admission to hospital, change in symptom score, change in Peak Flow (in children old enough to perform test)
Notes	Some children had difficulty triggering the Nebuhaler valve. Estimated SD for Peak Flow

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No details of dropouts.

Hussein 2002

Methods	Baseline characteristics: not stated
Participants	Setting: Alexandria, Egypt. Outpatient department study of children presenting with acute asthma of moderate severity. 60 children aged 2 - 12 years. Inclusion criteria: no details. Exclusion criteria: no details.
Interventions	Beta$_2$ -agonist: Salbutamol. Spacer: 'Large volume', up to 10 puffs of salbutamol given as single dose. Nebuliser: No details of nebuliser type, 0.15 mg/kg salbutamol given up to maximum of 5 mg. Driving gas not specified. Co-interventions: Not specified.
Outcomes	Admission to hospital, change in symptom score, pulmonary function, oxygen saturation, increase in heart rate. 4 admissions in nebuliser group and 3 in holding chamber group. Symptoms, oxygen saturation and lung function reported as similar in both groups, and mean heart rate higher in the nebuliser group
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No details of dropouts reported.

Idris 1993

Methods	Baseline characteristics: comparable. Intention-to-treat: not applicable. Power calculation: performed, predicted 90% power to detect 12% difference in lung function

Idris 1993 (*Continued*)

Participants	Setting: USA. Hospital Emergency Rooms. 35 participants aged 10 - 45 years, mean age 23 (spacer) and 25 (nebuliser). Mean PEF (% predicted) at presentation: spacer 34 (SD 14), nebuliser 37 (SD 17). Inclusion criteria: acute asthma. Exclusion criteria: angina, respiratory failure, COPD, smoking for 10 pack years or more, unable to perform spirometry
Interventions	Beta$_2$ -agonist: Salbutamol (Albuterol). Spacer: InspirEase. Dosage: 4 x 90 mcg puffs 1 puff every minute, inhaled by 1 slow inhalation. Treatment repeated every 30 minutes until FEV$_1$ was 80% predicted or participant asymptomatic or 6 treatments given. Nebuliser: T Up-Draft II Nebu-U-Mist. Dosage: 2.5 mg in 2 mL saline, driven by oxygen at 5 L/min. Treatment repeated every 30 minutes until FEV$_1$ was 80% predicted or participant asymptomatic or 6 treatments given. Dosage ratio: spacer/nebuliser = 1:7. Mean dose to max response with spacer 1.11 (SD 0.64) mg, nebuliser 7.63 (SD 3.9) mg. Co-interventions: parenteral steroids usually given within 1 hour of discharge
Outcomes	Further treatment (?admission), duration in emergency department, Peak Flow, FEV$_1$,FVC, heart rate, respiratory rate, administration of steroids
Notes	Results include % maximum response (see footnotes). Separate analysis for participants with FEV$_1$ < 30% predicted

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No details reported of withdrawals

Jamalvi 2006

Methods	Baseline characteristics: significantly higher PEF at baseline in spacer group
Participants	Setting: Emergency Room of the National Institute of Child Health in Karachi, Pakistan, from October 2000 to March 2001 150 children (aged 6 months to 15 years). 76% were classified as having severe asthma attack (24% mild or moderate) Inclusion criteria: acute asthma. Exclusion criteria: children requiring intensive care management, PEFR values under 20% or over 70% predicted, oxygen saturation under 90% in room air, or receiving daily systemic corticosteroids for more than 2 weeks before being seen in the emergency room
Interventions	Beta$_2$ -agonist: Salbutamol (Albuterol). Spacer: Babyhaler for younger children and spacer with mouthpiece for older children. Dosage: 2 x 100 mcg repeated 3 times at 20-minute intervals. Nebuliser: Type 2 Fleam Nuova S.P.A., Bresia, Italy. Dosage: 0.3 mg/kg with 2 mL Normal Saline repeated 3 times at 20-minute intervals. Dosage ratio: unknown. Co-interventions: none reported.
Outcomes	Admission to hospital, pulse, respiratory rate, BP, dyspnoea, cyanosis, wheeze, PEFR, clinical score, measured at 10 minutes, 20 minutes and 2 hours after completion of treatment
Notes	No details are given for mean age in each group or how many children were able to perform PEFR. Trial included as mean age is almost certainly over 2 years old

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	All participants accounted for in admission data. Three participants were excluded form the study

Kerem 1993

Methods	Baseline characteristics: comparable. Intention-to-treat analysis: not stated.
Participants	Setting: Canada. Emergency Department. 33 children aged 6 - 14 years old. Mean FEV_1 (% predicted) at presentation: spacer 40%, nebuliser 40%. Inclusion criteria: not stated. Exclusion criteria: critically ill, FEV_1 < 20% or > 70%, oxygen saturation in air < 92%, systemic steroids given for more than 2 weeks
Interventions	$Beta_2$ -agonist: Salbutamol (Albuterol). Spacer: VentAHaler. Dosage: 6 x 100 mcg (< 25 kg), 8 x 100 mcg (25 - 35 kg), 10 x 100 mcg (> 35 kg). Total dose discharged into spacer followed by 1 minute tidal breathing, Single treatment. Nebuliser: Whisper Jet, driven by oxygen at 6 - 10 L/min. Dosage: 0.15 mg/kg to maximum 5 mg given in 3 mL saline. Single Treatment. Dosage ratio: spacer/nebuliser = 1:5. Co-interventions: none.
Outcomes	Admission to hospital, symptom score, FEV_1, oxygen saturation, heart rate, respiratory rate
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available.
Allocation concealment (selection bias)	Low risk	Assigned by research pharmacist..
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No details of dropouts.

Leversha 2000

Methods	Baseline characteristics: comparable for asthma severity. Intention-to-treat: performed. Power calculation: powered to detect a difference of 1.25 in clinical score between groups
Participants	Setting: New Zealand. Emergency Department in children's hospital. 60 children aged 1 - 4 years; mean age 36 months (spacer) and 32 months. (nebuliser). 66% had received oral steroids in the previous 24 hours in each group. Inclusion criteria: Known history of asthma with a clinical score of greater than 3, presenting to ED with acute asthma. Exclusion criteria: bronchodilator given in the hour before presentation or requiring immediate admission to intensive care unit. Also co-existing medical condition (such as pneumonia)
Interventions	Beta$_2$ -agonist: Salbutamol (Albuterol) . Spacer: Aerochamber. Dosage: 6 x 100 mcg puffs inhaled separately by tidal breathing. Repeated every 20 minutes for a maximum of 6 treatments. Nebuliser: Marquest bowl with Hudson face mask. Dosage: 2.5 mg every 20 minutes for a maximum of 6 treatments, driven by wall oxygen. Double-dummy methodology so placebo given by the other route to all children. Co-interventions: supplemental oxygen if SaO_2 less than 92% and oral prednisone unless child had received oral steroids in past 24 hours. Dosage ratio: spacer/nebuliser = 1:4.
Outcomes	Admission to hospital. pulse, respiratory rate, SaO_2 , clinical score, tremor and hyperactivity measured 20 minutes after each treatment and 60 minutes after final treatment
Notes	Data in the paper is only provided for the results 20 minutes after the first treatment. One of the tables of data in the paper was inconsistent and has since been corrected. The data used in the review for heart rate and respiratory rate has been provided by Dr Leversha

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available.
Allocation concealment (selection bias)	Low risk	Pharmacy generated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.

Leversha 2000 (*Continued*)

Incomplete outcome data (attrition bias) Hospital Admission	Low risk	Three children were withdrawn, but were included in the analysis, (one from nebulizer group refused the nebulizer but was treated with spacer and discharged, and one from each group refused treatment and was admitted)

Lin 1995

Methods	Baseline characteristics: comparable. Intention-to-treat: not performed. Power calculation: not stated.
Participants	Setting: Taiwan. Hospital Emergency Department and paediatric allergy clinic. 111 children aged 5 - 16 years. Mean PEF (% predicted) at presentation: spacer 57 (SD 20)%, nebuliser 60 (SD 21)%. Inclusion criteria: acute asthma or acute exacerbation of chronic asthma. Exclusion criteria: inhaled beta$_2$ -agonist in previous 6 hours, unable to perform spirometry, pneumonia, congestive heart failure, foreign body aspiration, bronchopulmonary dysplasia
Interventions	Beta$_2$ -agonist: Terbutaline. Spacer: Aerochamber. Dosage: 3 x 0.25 mg puffs, each inhaled by 3 deep breaths. Single treatment. Nebuliser: Pulmo-Aide. Dosage: 2.5 mg in 2 mL saline, driven by air at 8 L/min. Single treatment. Dosage ratio: spacer/nebuliser = 1:3.5. Co-interventions: not stated.
Outcomes	Measured at 15 minutes after the start of treatment: symptom score, Peak, FEV$_1$, FVC, oxygen saturation, heart rate
Notes	Mean fall in SaO_2 at 15 minutes was 0.47 (SD 1.93)% in the nebuliser group, compared to a mean rise of 0.58 (SD 1.72)% in spacer group. Estimated SD for Peak Flow and pulse rate

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Alternate weeks.
Allocation concealment (selection bias)	High risk	Investigators had foreknowledge of treatment group assignment

Lin 1995 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	Six withdrawals (4 children on spacer and 2 on nebuliser refused treatment)

Maldano-Alanis 1997

Methods	Baseline characteristics: similar. Power calculation: "approximately 90%".
Participants	Setting: ER Hospital Infantil de Mexico Fredrico Gomez. 42 children aged 6 - 15; baseline FEV_1 69% (spacer) and 77% (nebuliser). Inclusion criteria: FEV_1 of 60% to 80% of predicted value. Exclusion criteria: use of xanthines, steroids, $beta_2$ -agonists or antihistamines. Unable to use spirometer
Interventions	$Beta_2$ -agonist: Salbutamol. Spacer: unknown. Dosage: 2 x 100 mcg twice 20 minutes apart. Nebuliser: Hudson driven by oxygen, dose 0.15 mg/kg up to maximum of 5 mg made up to 5 mL with saline. Given twice 20 minutes apart. Dose ratio up to 1:25.
Outcomes	FEV_1 at 1, 2, 3, 4, 5, 6 hours. Pulse rate rise. Symptoms using Silverman-Anderson scale.
Notes	No SDs reported. After 3 hours following treatment the spacer group FEV_1 had fallen significantly more than the nebuliser group

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.

Maldano-Alanis 1997 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	No withdrawals.

Morley 1988

Methods	Baseline Characteristics: Comparable. Intention-to-treat: not used.
Participants	Setting: Hospital inpatients, New Jersey, USA. 28 adults, admitted with acute status asthmaticus. Mean age of 34.8 (15.9) chamber group, 31.3 (19.0) nebuliser group. Inclusion criteria: acute status asthmaticus, admitted after failing multiple trials of either subcutaneous or nebulised beta$_2$ -agonists. Exclusion criteria: A smoking history of > 5 packs a year of cigarettes, emphysema, respiratory acidosis on admission, or pregnant. Unstable coronary insufficiency, recent myocardial infarction, or cardiac arrhythmia were also excluded
Interventions	Beta$_2$ -agonist: Salbutamol (Albuterol). Spacer: InspirEase, Key Pharmaceutical. Dosage: 3 inhalations (90 micrograms /inhalation) each separated by 5-minute intervals. Received every 4 hours. Nebuliser: Acorn 2 nebulizer (Marquest Medical Products Inc, Englewood, CO). Dosage: 0.5 mL (2.5 mg) albuterol and 2.0 mL normal saline solution nebulised over 15 min period. Received every 6 hours while awake. Additional therapies: All participants received standard IV dosages of aminophylline. IV methylprednisolone was administered as recommended by Haskell et al. No oral beta$_2$ -agonists were used. (Group 3 received 15 mg nebulised metaproterenol).
Outcomes	Spirometric improvement (FEV_1 and FVC) 15, 30, 60, 120, 180, 240 minutes following the 1st beta$_2$ -agonist treatment (best of 2 recorded), duration of hospital stay (discharge criteria: free of wheezing on auscultation and no exertional dyspnoea when walking on ground level), daily rates of spirometric improvement during course of hospitalisation (performed once in morning and once in afternoon at similar times every day,- just prior to treatment). Following 3rd day spirometry was not performed again until discharge (calculations were based on assumption of discharge day at day 6)
Notes	Trial begins from initial beta$_2$ -agonist dose given once admitted (at least 4 hours after last dose given in A+E.) No data of how much given before trial commenced. 3rd arm of this trial ignored as different beta$_2$ -agonist used

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Morley 1988 (*Continued*)

Random sequence generation (selection bias)	High risk	Alternate allocation.
Allocation concealment (selection bias)	High risk	Investigators had foreknowledge of treatment group assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	No withdrawals (however 2 participants' data were excluded from daily rates of spirometric improvement as spirometric analysis required was not completed)

Morrone 1990

Methods	Baseline characteristics: comparable. Intention to treat: not applicable.
Participants	Setting: Brazil. Mobile clinic. 44 adults, 36 women, 8 men. Mean PEF (% predicted) at presentation: 180 L/min (% predicted not stated). Inclusion criteria: PEF 120 - 200 L/min at presentation. Exclusion criteria: not stated.
Interventions	Beta$_2$ -agonist: Fenoterol. Spacer: 500 mL (type not stated). Dosage: 1 mg delivered as 200 mcg per minute inhaled by tidal breathing. Single treatment. Nebuliser: type not stated. Dosage: 2.5 mg in 3 mL saline driven by oxygen at 6 L/min. Single treatment. Dosage ratio: spacer/nebuliser = 1:2.5. Co-interventions: none.
Outcomes	Peak Flow. Actual readings changed to % predicted by assuming expected peak flow of 500 l/min as original data have been lost
Notes	Only the first part of this study compared spacer against nebuliser, the second part of the cross-over was not analysed due the high likelihood of contamination. Estimated SD for Peak Flow. Data were measured from graph published in errata. (Revista Paulista de Medicina 1990;108:98)

Morrone 1990 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Alternate allocation.
Allocation concealment (selection bias)	High risk	Investigators had foreknowledge of treatment group assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	All participants completed the study.

Parkin 1995

Methods	Baseline characteristics: Clinical asthma score was 5.7 chamber, 4.8 nebuliser (P = 0.02) therefore an adjusted mean used. Intention-to-treat analysis: performed. Power analysis: 30 in each group designed to detect approximately 90% difference in asthma score
Participants	Setting: Hospital inpatients (after stabilisation in Emergency Department), Canada. 60 children aged 1 - 5 years old (2.9 years mean) Inclusion criteria: moderate acute asthma. Exclusion criteria: not stated.
Interventions	Beta$_2$ -agonist: Salbutamol and ipratropium bromide. Spacer: Aerochamber 140 mL cylindrical with one-way valve and mask. Dosage: Salbutamol 400 mcg for those < 12 kg, 500 mcg for 12 - 16 kg, 600 mcg 16 kg or over. All had 40 mcg ipratropium bromide also. Nebulizer: Driven by compressed air, using a face mask Dosage: Salbutamol 0.15 mg/kg/dose (maximum 5 mg) + ipratropium bromide 125 micrograms, suspended in 3 mL of 0.9% saline over 15 minutes. Drug ratio: Assumed drug ratio of nebuliser : MDI and chamber as 1:4. Co-interventions: All participants received systemic corticosteroids.(IV vs or oral)
Outcomes	Primary outcome: 10-point clinical asthma score measuring: respiratory rate, wheezing, indrawing, observed dyspnoea, and inspiratory to expiratory ratio (Measured up to 60 hrs). Secondary measures:

Parkin 1995 (*Continued*)

	Time to discharge, time to 4-hourly dosing interval, total number of inhaled doses required, nurses assessed ease of administration and participants tolerance on a Likert scale, parents reported symptoms at 7 and 14 days post-discharge
Notes	Single blinding may have been appropriate due to age of participants i.e. little placebo effect in 1 - 5 year olds. Trial sponsored by Aerochamber and MDI companies. Study included as mean age over 2 years.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded.
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No details of withdrawals (9 children from spacer group crossed over to nebuliser). Four failures (stopping criteria not given)

Pendergast 1989

Methods	Baseline characteristics: compared. Intention-to-treat: not done. Power calculation: estimated 80%.
Participants	Setting: Australia. Acute presentation at Children's Hospital. 27 children aged 3 to 6.8 years. Mean symptom score at presentation: 2.13 (0.49) and 2.30 (0.46) in spacer groups, 2.42 (0.55) in nebuliser group. Inclusion criteria: not stated. Exclusion criteria: not stated.
Interventions	Beta$_2$ -agonist: Terbutaline. Spacer: Nebuhaler. Dosage: Low-dose group = 1 puff (0.25 mg) per 5 kg. High-dose group = 2 puffs (0.5 mg) per 5 kg. Each dose (bursts of 3 or 4 puffs) inhaled with 2 breaths and then a minute of tidal breathing.

Pendergast 1989 (*Continued*)

	Nebuliser: Unicorn. Dosage: 0.2 mg per kg weight in 2 mL saline (max 5 mg) driven by oxygen at 6L/min. Dosage ratio: spacer/nebuliser = 4:1 or 2:1. Co-interventions: none.
Outcomes	Admission to hospital, symptom score.
Notes	Withdrawals: 3 from spacer group due to inability to co-operate and 1 from spacer group due to clinical deterioration. Vague descriptions of outcome ("no difference" between number in each group needing a second treatment or admission to hospital). Lower-dose spacer group showed a trend to deterioration on score between 30 and 60 minutes after treatment which did not reach significance (P = 0.05)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.
Incomplete outcome data (attrition bias) Hospital Admission	High risk	4 children withdrawn from spacer group (3 could not use the nebuhaler and one deteriorated in clinical state)

Ploin 2000

Methods	Baseline characteristics: SaO_2 was significantly lower in the Holding Chamber group. Intention-to-treat analysis: yes. Power analysis: yes.
Participants	Setting: Paediatric Emergency Department of 2 teaching hospitals in Lyon, France. 64 children recruited aged 1 - 5 years; mean ages 24.8 months (chamber) and 25.5 months (nebuliser). 1 child excluded from the analysis due to being randomised twice. Inclusion criteria: Acute wheezing in children with at least 3 episodes of wheezing or 3 episodes with a family history of atopy, eczema or asthma. Exclusion criteria: SaO_2 less than 90%, inhaled or systemic steroids within the past 24 hours, or underlying chronic disease

Ploin 2000 (*Continued*)

Interventions	Beta$_2$ -agonist: Salbutamol (Albuterol). Spacer: Babyhaler. Dosage: 50 mcg/kg (maximum of 10 puffs) each puff followed by 8 breaths over 1 - 2 minutes. Treatment given at 20-minute intervals for 60 mins. Nebuliser: Ultrasonic (ARP 70) used in room air. Dosage: 150 mcg/kg diluted in 4 mL Saline over 8 - 9 minutes. Repeated at 20-minute intervals. Dose ratio: spacer:nebuliser = 1:3. Duration 60 minutes and double-dummy design.
Outcomes	Change in pulmonary index, hospital admission, ease of use, improvement in SaO_2
Notes	Clarification of inclusion criteria, and reasons for hospital admission provided by the author. Study included as the mean age was over 2 years and care was taken to exclude children with viral bronchiolitis

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Blocks of 4 computer-generated.
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	"None of the patients dropped out of the study".

Raimondi 1997

Methods	Baseline characteristics: comparable. Intention-to-treat: not stated. Power calculation: carried out but in the event the study was underpowered
Participants	Setting: Argentina, Emergency Department at Hospital Ferrer, Buenos Aires. 27 adults with asthma according to the ATS criteria. Inclusion criteria: severe asthma attack defined as FEV_1 < 1 litre or < 30% predicted. Exclusion criteria: smokers, pregnant, pneumothorax, pneumonia or in extremis

Raimondi 1997 (*Continued*)

Interventions	Beta$_2$ -agonist: Salbutamol (Albuterol). Spacer: Aerochamber. Dosage: 400 mcg delivered as 4 separate actuations, each one inhaled by 3 deep breaths and repeated at 60-second intervals. Repeated every 30 minutes for 2 hours and then hourly until the 6th hour. Nebuliser: Puritan-Bennett Raindrop. Dosage: 5 mg given over 5 to 10 minutes and repeated as above. Dose Ratio: spacer:nebuliser = 1:13. Co-interventions: all participants received 8 mg Dexamethasone IV and were given oxygen
Outcomes	FEV$_1$, hospital admission.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	No withdrawals

Rao 2002

Methods	Baseline characteristics: comparable. Intention-to-treat: not stated. Power calculation: not stated.
Participants	Setting: Pakistan, Hospital Emergency Departments in 2 hospitals in Karachi. 50 adults aged 18 - 62, (mean age 40), with acute asthma exacerbation (moderate to severe according to BTS guidelines). Initial mean PEF 27 - 30% predicted. Inclusion criteria: acute asthma defined by signs, symptoms and peak flow readings. Exclusion criteria: unable to perform spirometry, history of respiratory failure, COPD, IHD or arrhythmias, smoking history of more than 10 pack years or pregnancy

Rao 2002 (*Continued*)

Interventions	Beta$_2$ -agonist: Salbutamol. Spacer: Not specified. Dosage: 4 x 100 mcg 1 puff every minute for 4 doses repeated at 30-minute intervals until participant improved or FEV_1 rose to 70% predicted or 3 doses had been administered. Nebuliser: Not specified. Dosage: 2.5 mg in 2.5 mL saline driven by oxygen at 5 L to 6 L per minute, given at 30-minute intervals until participant improved or FEV_1 rose to 70% predicted or 3 doses had been administered. Dosage ratio: spacer;nebuliser 1:6. Co-interventions: not specified.
Outcomes	FEV_1 , PEF, FVC, and pulse rate at 30 and 60 minutes. Hospital admission. After the first treatment 17 spacer participants and 13 nebuliser participants improved and did not require the second or third treatments
Notes	16% of participants in each group were smokers, and none was taking inhaled therapy at presentation. SD for change in FEV_1 based on published absolute SD (conservative estimate)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No details of dropouts.

Robertson 1998

Methods	Baseline characteristics: comparable. Intention-o-treat analysis: children requiring additional therapy were excluded from further analysis. Power analysis: none.

Robertson 1998 (*Continued*)

Participants	Setting: Australia, multicentre in Emergency Departments. 155 children recruited aged 4 - 12 years, 147 evaluable. Inclusion criteria: PEF under 70% predicted (aged over 7) or clinical score of > 4 out of 12. Exclusion criteria: critically ill, concurrent cardiopulmonary disease or given bronchodilator within the last hour
Interventions	Beta$_2$ -agonist: Salbutamol. Spacer: Volumatic. Dosage: 600 mcg (under 25 kg) and 1200 mcg (over 25 kg) given in bursts of 3 puffs with 15 seconds of tidal breathing. Nebuliser: AVA-NEB Hudson. Dosage: 2.5 mg (< 25 kg) or 5 mg (> 25 kg) in 2.5 mL saline driven by oxygen at 8 to 10 L/min. Dose ratio spacer:nebuliser = 1:4.2. Single-dose study.
Outcomes	Withdrawal to further treatment, PEF, pulse, blood pressure, tremor and symptom score
Notes	15 withdrawals in spacer group and 12 in nebuliser group. Both groups showed 1% increase in SaO_2 . The study was funded by Allen and Hanbury's

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	27 withdrawals due to inadequate response (15 from spacer group and 12 from nebuliser group)

Rodrigo 1993

Methods	Baseline characteristics: comparable. Intention-to-treat: not stated. Power calculation: not stated.
Participants	Setting: Uruguay. Hospital Emergency Room. 97 adults aged 18 - 50. Mean PEF(% predicted) at presentation: 32% in each group. Inclusion criteria: "criteria of the American Thoracic Society". Exclusion criteria: PEF or FEV_1 > 50% predicted pregnancy, history of chronic cough, other medical disease
Interventions	$Beta_2$ -agonist: Salbutamol. Spacer: Volumatic. Dosage: 4 x 100 mcg every 10 minutes, each puff inhaled with 2 deep inhalations from the spacer. Nebuliser: Ava-Neb. Dosage: 1.5 mg in 4 mL saline driven by oxygen at 8 L/min at 15-minute intervals. Dosage ratio: spacer:nebuliser = 1:2, (mean total dose 5.61 mg/11.8 mg). Co-interventions: oxygen by nasal prongs 4 L/min given to all participants. All participants received oral steroids at discharge
Outcomes	Admission to hospital, duration in Emergency Department, Peak Flow, FEV_1, FVC, heart rate, development of tremor
Notes	Separate analysis was performed on those participants admitted and those with FEV_1 < 0.9 L. Estimated SD for final Peak Flow in holding chamber group

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table.
Allocation concealment (selection bias)	Unclear risk	Infomation not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No details of dropouts reported.

Rodrigo 1998

Methods	Baseline characteristics: comparable. Intention-to-treat: no data. Power calculation: powered to detect a 36% difference (0.6 litres) in FEV_1
Participants	Setting: Uruguay, Hospital Emergency Room in Montevideo. 22 adults aged 18 - 50 with acute asthma exacerbation (all met ATS criteria for asthma) . Initial mean PEF 30% predicted and SaO_2 95%. Inclusion criteria: PEF and FEV_1 both below 50% predicted at presentation. Exclusion criteria: other chronic disease or pregnancy.
Interventions	$Beta_2$ -agonist: Salbutamol. Spacer: Volumatic. Dosage: 4 x 100 mcg every 10 minutes, (2.4 mg per hour) Nebuliser: Hudson T Up-draft flow rate 8 L/min. Dosage: 1.5 mg in 4 mL saline driven by compressed air at 8 L/min at 15-minute intervals. Dosage ratio: spacer;nebuliser = 1:2.3. Co-interventions: oxygen was allowed in the protocol if SaO_2 fell below 90% but was not required in any participant. 500 mg of hydrocortisone was given to all participants with a poor response after 3 hours
Outcomes	FEV_1 , PEF, QTc interval, SaO_2 (arterial oxygen saturation) every 30 minutes. Potassium and Salbutamol blood levels at start and 3 hours
Notes	Neither group showed a deterioration in oxygen saturation and no oxygen was needed in this study. Final plasma salbutamol was 10.1 (SD 1.6 ng/m) in spacer group and 14.4 (SD 2.3 ng. mL) in nebuliser group

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No details of dropouts reported.

Rodriguez 1999

Methods	Baseline characteristics: similar in the 2 groups. Intention-to-treat: not required. Power calculation: not stated.
Participants	Setting: Colombia. Hospital Emergency Department (University Hospital of San Ignatio). 69 adults (56 women) mean age 39 years. Mean PEF at baseline 186 L/min, SD 78 L/min (spacer group) and 179 L/min SD 89 L/min (nebuliser group). Asthma severity: 26 mild asthma attack, 20 moderate and 23 severe. Inclusion criteria: "acute exacerbation of asthma" defined clinically. Exclusion criteria: no details.
Interventions	Beta$_2$ -agonist: Salbutamol. Spacer: Volumatic. Dosage: 4 x 100 mcg every 10 minutes for 1 hour (no details of inhalation method). Nebuliser: type not stated. Dosage: 2.5 mg every 20 minutes for 1 hour. Dosage ratio: spacer:nebuliser = 1:3. Co-interventions: not stated.
Outcomes	Admission to hospital. heart rate, respiratory rate, PEF, every 20 minutes and at 120 minutes. Blood gases at baseline and 120 minutes
Notes	Unpublished data supplied by authors. SDs provided for each time period, and imputed to the change measurements

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	High risk	Allocation not concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes evaluated by an observer blinded to the treatment allocated
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	No withdrawals reported on correspondence with the authors

Salzman 1989

Methods	Baseline characteristics: comparable, except baseline FEV_1 lower in the spacer group. Intention-to-treat: not done. Power calculation: not stated.
Participants	Setting: USA. Hospital Emergency Department. 44 adults. Spacer group mean age 32.5 yrs (SD 12.5), nebuliser group mean age 28 yrs (SD 10.3). Mean FEV_1 (% predicted) at presentation: Spacer 26% (SD 12.1%), nebuliser 33% (SD 16%). Inclusion criteria: acute asthma FEV_1 < 50% predicted. Exclusion criteria: COPD, pneumothorax, depression, $PaCO_2$ > 40, ventilation required
Interventions	Beta$_2$ -agonist: Metaproterenol sulphate. Spacer: Aerochamber. Dosage: 3 x 0.65 mg puffs each 5 minutes apart. Single treatment. No details of breathing method. Nebuliser: type not stated. Dosage: 15 mg in 2 mL saline over 10 minutes. Single treatment. Dosage ratio: spacer: nebuliser = 1:8. Co-interventions: none.
Outcomes	Admission to hospital, FEV_1, FVC, heart rate, respiratory rate
Notes	Rise in FEV_1 (% predicted) calculated from data given in paper

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	Six withdrawals. No participant was removed from the study because of worsening clinical status

Sannier 2007

Methods	Excluded: 106 of 185 children presenting during working hours were excluded. Withdrawals: none for the initial study, 6 families were lost to longer-term follow-up. Baseline characteristics: comparable, except imbalance in respiratory rate
Participants	Setting: Paediatric Emergency Department in France . 79 children aged 4 - 15 years (mean age 9 years). 40 participants allocated to nebuliser and 39 allocated to spacer. Inclusion criteria:severe acute exacerbation of asthma (Bishop score > 6 or SaO_2 less than 92%). The definition of severe asthma was understood as an acute attack developing over more than 24 hours (or nocturnally), non-responsive to $beta_2$ -agonist therapy (initiated prior to hospital presentation), or occurring in spite of maintenance treatment with inhaled steroids (+/- $beta_2$ -agonist), or recurring within 1 month of oral steroid treatment and an attack occurring in a child with previous treatment in intensive care for acute asthma**.**
Interventions	$Beta_2$ -agonist: Salbutamol or Terbutaline Spacer: Babyhaler/Volumatic or Nespacer/Nebuhaler (according to child's home use). Dosage: 6 x 100mcg salbutamol or 6 x 250mcg terbutaline every 20 minutes for 6 doses (each inhalation was separated by 8 - 10 valve movements). Nebuliser: Mininebuliser AIRVIE, Peters, Bobigny, France. Driven by oxygen at 6 L/min. Dosage: 0.15 mg/kg salbutamol in 4 mL saline every 20 minutes for 6 doses (minimum 1.5 mg to maximum 5 mg per dose). Dosage ratio: spacer:nebuliser = 1:3 to 1:5. Co-interventions: all participants received oral steroids at the start of treatment
Outcomes	Hospitalisation, pulse rate, respiratory rate, SaO_2 , PEF.
Notes	Baseline imbalance in respiratory rate noted, which may have contributed to the larger fall in the nebuliser group

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details.
Allocation concealment (selection bias)	Low risk	"numbered envelopes".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.

Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No description of withdrawals during the initial treatment period

Turner 1988

Methods	Excluded: 26 out of 101 evaluated. Baseline characteristics: comparable. Intention-to-treat: not stated. Power calculation: not stated.
Participants	Setting: USA. Hospital Emergency Room. 53 adults with asthma 18 - 75 years old, 22 participants with COPD also in study but excluded from this review. Mean FEV_1 at presentation: spacer 1.2 L (SD 0.1), nebuliser 1.1 L (SD 0.1). Inclusion criteria: onset symptoms < 30 years or < 10 pack years smoking. Exclusion criteria: pregnancy, suspected MI or CCF, intubation required
Interventions	$Beta_2$ -agonist: Metaproterenol. Spacer: Inspirease. Dosage: 3 x 0.65 mg puffs at 2-minute intervals inhaled by 2 slow inhalations each. Total of 3 treatments at 30-minute intervals. Nebuliser: Acorn II. Dosage: 15 mg in 2 mL saline given over 10 minutes. Total of 3 treatments at 30-minute intervals. Dosage ratio: spacer:nebuliser = 1:8. Co-interventions: oxygen and intravenous steroids given at the discretion of the emergency room physician who was not involved in the study
Outcomes	Admission to hospital, symptom score, FEV_1 , oxygen saturation, heart rate, respiratory rate, administration of steroids
Notes	SDs calculated from raw data supplied by the author. Predicted Peak Flow estimated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.

Turner 1988 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy.
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No details of dropouts reported.

Valencia 1999

Methods	Baseline characteristics: comparable. Intention-to-treat: not stated. Power calculation: not stated.
Participants	Setting: Casualty Department of Children's hospital in Columbia. 70 children with acute asthma aged from 1 - 6 years old, mean age 3.2 years (spacer) and 3.6 years (nebuliser). Mean oxygen saturation 92% (spacer) and 91% (nebuliser). Inclusion criteria: acute asthma exacerbation. Exclusion criteria: not stated.
Interventions	Beta$_2$ -agonist: Salbutamol. Spacer: Type unspecified (500 mL size). Dosage: 2 x 100mcg given 3 times at 20-minute intervals. Nebuliser: Breath Neb II. Dosage: 0.15 mg/kg diluted in 4 mL of saline, given 3 times at 20-minute intervals. Dosage ratio: not stated. Co-interventions: not stated.
Outcomes	Respiratory rate, oxygen saturation, participant rating, clinical response all after 60 minutes
Notes	Paper states that 2 doses of 100 mg were given via spacer but this has been assumed to be a misprint for 100 mcg

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Used True-epistat to assign treatment groups.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias)	High risk	Open study.

Valencia 1999 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No details of dropouts reported.

Vazquez 1992

Methods	Baseline characteristics: comparable. Intention to treat: not stated. Power calculation: not stated.
Participants	Setting: Spain. Hospital Emergency Room. 18 children with asthma. Mean age 9.33 years (spacer), 8.66 years (nebuliser). Mean FEV_1 (% predicted): spacer 41.3% (SD 16%), nebuliser 39.6%(SD 19%) . Inclusion criteria: FEV_1 less than 65% predicted and no beta-agonist given in the previous 2 hours
Interventions	$Beta_2$ -agonist: Salbutamol. Spacer: Volumatic. Dosage: 5 x 100 mcg together into spacer followed by 30 seconds of tidal breathing. Followed by 10 x 100 mcg every 20 minutes until stable or 1.5 mg/kg maximum dose. Nebuliser: Type not stated. Dosage: 500 mcg diluted in 3 mL driven by oxygen at 7 L/min. Dosage ratio: spacer:nebuliser = 1.3:1 Total average dose by spacer 3.2 mg (SD 1) and by nebuliser 2.5 mg (SD 0.7). Co-interventions: not stated.
Outcomes	Admission to hospital, peak flow, FEV_1 , FVC, oxygen saturation, heart rate
Notes	Improvement in lung function expressed as % maximum predicted (see footnote). No significant changes in blood gases in either group.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available.
Allocation concealment (selection bias)	Unclear risk	Informaion not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.

Vazquez 1992 (*Continued*)

Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No details of dropouts reported.

Vivek 2003

Methods	Baseline characteristics: "comparable". Power calculation: not stated.
Participants	Setting: South India. Emergency Room. 122 adults and children aged 10 - 50 years. 54 participants allocated to nebuliser and 68 allocated to spacer. Mean PEF at presentation: 200 - 250 L/min. Inclusion criteria:acute exacerbation of asthma (PEF 200 - 250 L/min). Exclusion criteria: not stated.
Interventions	Beta$_2$ -agonist: Terbutaline. Spacer: Astra Spacehaler (750 mL). Dosage: 6 puffs of 0.25 mg. Treatment repeated at 5 and 30 minutes. Each puff inhaled separately. Nebuliser: Aerofamily nebuliser. Dosage: 5 mg (0.5 mL respirator solution + 1.5 mL normal saline). Treatment repeated at 5 and 30 minutes. Dose ratio: spacer:nebuliser = 1:4. Duration 60 minutes.
Outcomes	Endpoint: Terbutaline doses were administered until: 1. PEFR increased to 250 l/min, or 2. Participant becomes asymptomatic, or 3. 3 doses of terbutaline given, or 4. Side effects/clinical deterioration occurred.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study.

Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No details of withdrawals.

Williams 1996

Methods	Baseline characteristics: comparable. Intention-to-treat analysis: not required.
Participants	Denver, USA. Urban paediatric Emergency Department. 60 children aged 6 years or older. Mean PEF at presentation 46% predicted. Inclusion criteria: past history of asthma or current reversibility with albuterol. Exclusion criteria: corticosteroid therapy in the past 7 days, chronic cardiopulmonary disease other than asthma and severe presentation (depressed mental status, cyanosis, impending respiratory failure)
Interventions	Beta$_2$ -agonist: Salbutamol (Albuterol). Spacers: Aerochamber (20 participants) and ACE (22 participants), 4 x 90 mcg actuations of salbutamol given separately every 30 minutes, inhaled using tidal breathing for 1 minute each. 3 treatments given at 30-minute intervals. Nebuliser: PARI-JET II 2.5 mg of Albuterol given every 30 minutes in 3 mL saline driven by pressurised air at 6 L per minute. 3 treatments given at 30-minute intervals. Co-interventions: oxygen was given to all participants with an oxygen saturation of less than 92% while breathing room air. All participants were given oral prednisolone at a dose of 2 mg/kg (maximum 60 mg) within 30 minutes of enrolment
Outcomes	Admission to hospital, change in % predicted peak flow, change in % predicted respiratory rate
Notes	The results for the 2 spacers were pooled. 4 participants required additional treatment in the emergency department with 1 - 3 further treatments with nebulised albuterol before they were discharged; these were 1 from the nebuliser group and 3 from the spacer groups

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.

Williams 1996 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The physician investigator remained blind to the delivery system
Incomplete outcome data (attrition bias) Hospital Admission	Low risk	All participants completed the study.

Yasmin 2012

Methods	Baseline characteristics: comparable. Intention-to-treat analysis: not required. Home-made non-valved spacers were made by cutting off the top of a 500 mL water bottle and making a hole in the bottom of the bottle for the MDI
Participants	Dhaka Medical College, Bangladesh, recruited children between 2 and 12 years old between April 2007 and March 2008 with acute exacerbation of asthma. 8 of 58 children were excluded as they had life-threatening attacks of asthma. All children were given oxygen and intravenous hydrocortisone (4 mg/kg)
Interventions	3 treatments given at 20-minute intervals (25 children in each group) 1. 6 puffs of Salbutamol via MDI and home-made spacer. 2. Nebulised salbutamol solution (0.15 mg/kg and minimum 2.5 mg) in 2.5 mL normal saline Dose ratio: variable.
Outcomes	Outcomes were evaluated 20 minutes after each treatment and oxygen saturation after the third dose. Change in oxygen saturation, respiratory rate, heart rate and wheeze were measured. Those who did not show signs of improvement were withdrawn and treated in the inpatient department. Adverse events of tremor, palpitations and vomiting were reported
Notes	Number of admissions to hospital in each group were not reported in the paper, and we did not assume that those who were described as having poor responses to treatment were necessarily admitted. Due to discrepancies in the data reported in Table II in the paper, we have not been able to incorporate data on SaO_2 , heart rate and respiratory rate. Clarification from the Journal Editor has been sought, but no reply has been received

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Simple random number with the help of envelopes.
Allocation concealment (selection bias)	Unclear risk	Simple random number with the help of envelopes.

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No indication that assignment was concealed from those assessing the children
Incomplete outcome data (attrition bias) Hospital Admission	Unclear risk	No description of dropouts. Eight excluded due to life threatening asthma,pneumonia, congenital heart disease or heart failure

% max predicted - (post-treatment - basal)/(predicted - basal); ATS - American Thoracic Society; BTS - British Thoracic Society; CCF - congestive cardiac failure; COPD - Chronic obstructive pulmonary disease; DPI - dry powder inhaler; ED - Emergency Department; ER - Emergency Room; FEV_1 - Forced expiratory volume in one second; IHD - ischaemic heart disease; IV - intravenous; FVC - forced vital capacity; ITT - intention-to-treat; MDI - metered-dose inhaler; MI - myocardial infarction; NAEPP- National Asthma Education and Prevention Program; PEF(R) - Peak expiratory flow (rate); puff - actuation of metered-dose inhaler; SaO_2 - saturated oxygen level; SD - standard deviation.

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

Study	Reason for exclusion
Beasley 1985	Probably hospitalised participants and no response from authors to request for further information
Benton 1989	Not randomised.
Berenberg 1985	Mixed population of participants, not possible to separate data from asthmatics and no response from authors
Campbell 1995	No randomisation.
Deerojanawong 2005	Mean age of children was under 2 years.
Fayaz 2009	Not a randomised trial.
Fuglsang 1986	Cross-over design inappropriate for acute asthma.
Hart 2009	Preliminary study in 8 adults who were not clearly suffering from acute asthma
Hodder 1988	No outcomes presented in this abstract in a form that could be used. No response from author
Jasper 1987	Mixed population of participants, not possible to separate data from asthmatics and no response from authors

(*Continued*)

Kaashmiri 2010	Study in infants under 2 years of age.
Levitt 1995	Mixed population of COPD and asthma; no separate data given for asthmatic participants. No response from author
Madsen 1982	No useable data and no response from authors.
Maguire 1991	Probably hospitalised patients, no response from authors to request for clarification
Mandelberg 1997	Mixed population of COPD and asthma; no separate data given for asthmatic patients. No response from author
Mandelberg 2000	Infants and young children with a median age of 16 months.
Morgan 1982	No standard deviation published in paper and no reply from authors. No useable data
Newman 2002	Non-randomised (before-and-after study).
Rubilar 2000	Study in infants of 1 - 24 months.
Shaikh 2001	Not acute asthma.
Shim 1984	Not acute asthma.
Summer 1989	Different beta$_2$ -agonists used.
Tarala 1980	No holding chamber used.
Vilarinho 2003	Not acute asthma. Children using bronchodilators or corticosteroids were excluded
Wildhaber 1999	Not acute asthma.

DATA AND ANALYSES

Comparison 1. Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admission	18		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Adults	9	582	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.61, 1.43]
1.2 Children	9	757	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.47, 1.08]
2 Hospital admission or poor response to treatment	21		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Adults	9	582	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.61, 1.43]
2.2 Children	12	937	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.33]
3 Duration in emergency department (minutes).	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Adults	2	132	Mean Difference (IV, Random, 95% CI)	1.75 [-23.45, 26.95]
3.2 Children	3	396	Mean Difference (IV, Random, 95% CI)	-33.48 [-43.32, -23.65]
4 Final rise in FEV_1 (% predicted)	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Adults	6	307	Mean Difference (IV, Fixed, 95% CI)	0.96 [-2.54, 4.46]
4.2 Children	2	48	Mean Difference (IV, Fixed, 95% CI)	0.92 [-4.96, 6.79]
5 30 minute rise in FEV_1 (% predicted)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Adults	3	200	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-3.18, 2.78]
6 Severe asthmatics final rise in FEV_1 (% predicted)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Adults	4	94	Mean Difference (IV, Fixed, 95% CI)	1.60 [-4.49, 7.69]
7 Final rise in peak flow (% predicted)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Adults	3	139	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-4.60, 3.63]
7.2 Children	3	166	Mean Difference (IV, Fixed, 95% CI)	-2.99 [-8.88, 2.91]
8 30 minute rise in peak flow (% predicted)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Adults	2	147	Mean Difference (IV, Fixed, 95% CI)	0.92 [-2.68, 4.51]
9 Rise in pulse rate (% baseline)	16		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Adults	7	376	Mean Difference (IV, Random, 95% CI)	-1.23 [-4.06, 1.60]
9.2 Children	9	670	Mean Difference (IV, Random, 95% CI)	-5.41 [-8.34, -2.48]
10 % Oxygen saturation (change from baseline)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Adults	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Children	6	476	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.61, 0.24]
11 Number of participants developing tremor	8		Risk Ratio (IV, Random, 95% CI)	Subtotals only
11.1 Adults	4	234	Risk Ratio (IV, Random, 95% CI)	0.82 [0.28, 2.37]
11.2 Children	4	254	Risk Ratio (IV, Random, 95% CI)	0.64 [0.44, 0.95]
12 Number of participants given steroids	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Adults	2	88	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.08, 6.02]

12.2 Children	2	297	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.95, 1.32]
13 Rise in respiratory rate (breaths per minute)	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
13.1 Adults	5	257	Mean Difference (IV, Random, 95% CI)	0.28 [-2.29, 2.84]
13.2 Children	8	686	Mean Difference (IV, Random, 95% CI)	-0.94 [-2.84, 0.97]

Comparison 2. Spacer (chamber) versus nebuliser (single-treatment studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admission	5		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Children	4		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Final peak flow (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 30 minute rise in FEV$_1$ (% predicted)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 15 minute rise in FEV$_1$ (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 30 minute rise in peak flow (% predicted)	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Children	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 15 minute rise in peak flow (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Rise in pulse rate (% baseline)	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Children	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Number of participants developing tremor	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Number of participants with deterioration in blood gases	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Children	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Rise in respiratory rate	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Spacer (chamber) versus nebuliser (inpatient studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of hospital admission (days)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Adults	1	18	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-3.23, 2.03]
1.2 Children	2	75	Mean Difference (IV, Fixed, 95% CI)	0.33 [-0.10, 0.76]
2 Number of hours until reached 4-hourly dosing regimen	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Total number of inhaled doses received	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Number of participants returning to normal PEFR and respiratory score levels (end of study)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Number of symptom-free participants 14 days post-discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Readmissions in the subsequent 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Clinical asthma score (end of trial)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Maximum percentage decrease in respiratory score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Respiratory rate at discharge	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Adults	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Children	2	75	Mean Difference (IV, Fixed, 95% CI)	-0.91 [-3.20, 1.38]
10 Heart rate at discharge	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Adults	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Children	2	76	Mean Difference (IV, Fixed, 95% CI)	1.06 [-5.48, 7.61]
11 Oxygen saturations at discharge	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 Adults	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Children	2	76	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.42, 0.66]
12 30 minute rise in FEV_1	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Adults	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

12.2 Children	1	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Final rise in FEV1	2	Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Adults	1	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Children	1	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Final rise in peak flow (% change from baseline)	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 Adults	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Children	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admission	16		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Adults with other spacers	6	366	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.55, 2.84]
1.2 Adults with Volumatic	2	166	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.51, 1.38]
1.3 Children with other spacers	6	515	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.39, 0.96]
1.4 Children with Volumatic	2	163	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.05, 6.11]
2 Hospital admission or poor response to treatment	19		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Adults with other spacers	6	366	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.55, 2.84]
2.2 Adults with Volumatic	2	166	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.51, 1.38]
2.3 Children with other spacers	8	635	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.55, 1.16]
2.4 Children with Volumatic	3	223	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.79, 2.13]
3 Duration in emergency department (minutes).	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Adults with other spacers	1	35	Mean Difference (IV, Random, 95% CI)	-9.0 [-42.91, 24.91]
3.2 Adults with Volumatic	1	97	Mean Difference (IV, Random, 95% CI)	15.00 [-22.65, 52.65]
3.3 Children with other spacers	2	348	Mean Difference (IV, Random, 95% CI)	-29.89 [-40.47, -19.32]
4 Final rise in FEV1 (% predicted)	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Adults with other spacers	3	168	Mean Difference (IV, Fixed, 95% CI)	0.30 [-4.70, 5.30]
4.2 Adults with Volumatic	2	119	Mean Difference (IV, Fixed, 95% CI)	1.20 [-4.13, 6.53]
4.3 Children with other spacers	1	30	Mean Difference (IV, Fixed, 95% CI)	0.0 [-6.17, 6.17]
4.4 Children with Volumatic	1	18	Mean Difference (IV, Fixed, 95% CI)	9.8 [-9.41, 29.01]
5 30 minute rise in FEV1 (% predicted)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Adults with other spacers	1	53	Mean Difference (IV, Fixed, 95% CI)	-3.80 [-8.51, 0.91]
5.2 Adults with Volumatic	1	97	Mean Difference (IV, Fixed, 95% CI)	1.5 [-3.07, 6.07]
6 Severe asthmatics final rise in FEV1 (% predicted)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Adults with other spacers	3	55	Mean Difference (IV, Fixed, 95% CI)	0.86 [-6.77, 8.48]
6.2 Adults with Volumatic	1	39	Mean Difference (IV, Fixed, 95% CI)	2.90 [-7.21, 13.01]

7 Final rise in peak flow (% predicted)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Adults with Volumatic	2	119	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-4.77, 3.98]
7.2 Children with other spacers	2	148	Mean Difference (IV, Fixed, 95% CI)	-3.75 [-9.95, 2.45]
7.3 Children with Volumatic	1	18	Mean Difference (IV, Fixed, 95% CI)	4.10 [-14.81, 23.01]
8 30 minute rise in peak flow (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Adults with Volumatic	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Rise in pulse rate (% baseline)	13		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Adults with other spacers	3	168	Mean Difference (IV, Fixed, 95% CI)	-2.28 [-7.81, 3.24]
9.2 Adults with Volumatic	3	188	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-3.89, 3.58]
9.3 Children with other spacers	5	464	Mean Difference (IV, Fixed, 95% CI)	-6.80 [-9.14, -4.45]
9.4 Children with Volumatic	2	78	Mean Difference (IV, Fixed, 95% CI)	-6.73 [-11.24, -2.23]

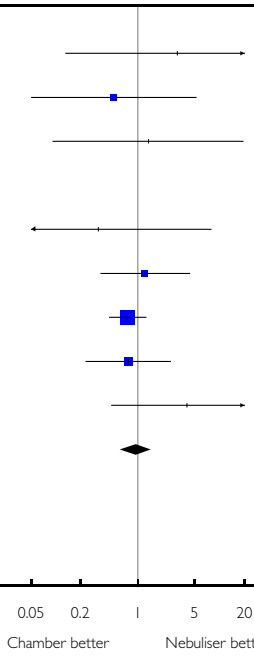
Analysis 1.1. Comparison 1 Spacer (chamber) versus nebuliser (multiple-treatment studies), Outcome 1 Hospital admission.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome: 1 Hospital admission

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adults					
Colacone 1993	1/40	0/40		1.5 %	3.00 [0.13, 71.51]
Dhuper 2008	1/29	2/29		6.1 %	0.50 [0.05, 5.21]
Idris 1993	1/15	1/20		2.6 %	1.33 [0.09, 19.64]
Raimondi 1997	0/9	0/9			Not estimable
Rao 2002	0/25	1/25		4.6 %	0.33 [0.01, 7.81]
Rodrigo 1993	5/49	4/48		12.3 %	1.22 [0.35, 4.29]
Rodriguez 1999	14/36	17/33		54.0 %	0.75 [0.45, 1.28]
Turner 1988	4/27	5/26		15.5 %	0.77 [0.23, 2.56]
Vivek 2003	5/68	1/54		3.4 %	3.97 [0.48, 32.98]
Subtotal (95% CI)	**298**	**284**		**100.0 %**	**0.94 [0.61, 1.43]**
Total events: 31 (Holding Chamber), 31 (Nebuliser)					
Heterogeneity: Chi^2 = 3.99, df = 7 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 0.29 (P = 0.77)					



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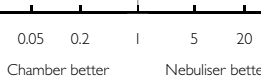
Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 Children					
Chong-Neto 2005	0/20	0/10			Not estimable
Chou 1995	4/71	5/81		11.4 %	0.91 [0.25, 3.27]
Direkwatanachai 2008	1/68	2/77		4.6 %	0.57 [0.05, 6.11]
Jamalvi 2006	4/84	7/66		19.1 %	0.45 [0.14, 1.47]
Leversha 2000	10/30	18/30		43.8 %	0.56 [0.31, 1.00]
Ploin 2000	3/31	3/32		7.2 %	1.03 [0.23, 4.73]
Sannier 2007	6/39	3/40		7.2 %	2.05 [0.55, 7.63]
Vazquez 1992	0/9	0/9			Not estimable
Williams 1996	2/42	2/18		6.8 %	0.43 [0.07, 2.81]
Subtotal (95% CI)	**394**	**363**		**100.0 %**	**0.71 [0.47, 1.08]**
Total events: 30 (Holding Chamber), 40 (Nebuliser)					
Heterogeneity: Chi^2 = 4.45, df = 6 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 1.61 (P = 0.11)					
Test for subgroup differences: Chi^2 = 0.85, df = 1 (P = 0.36), I^2 =0.0%					



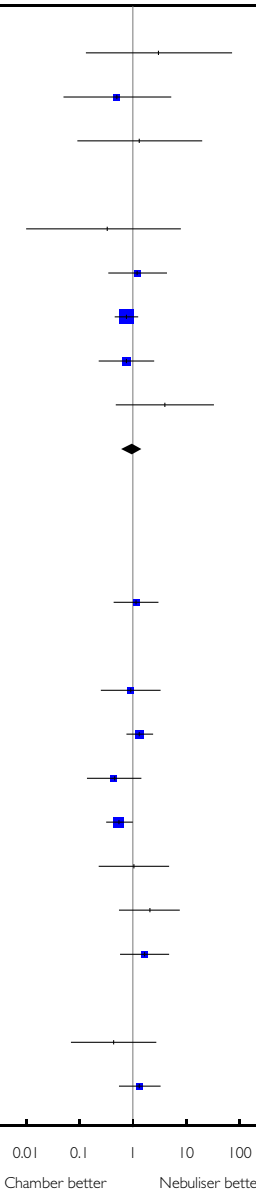
Analysis 1.2. Comparison 1 Spacer (chamber) versus nebuliser (multiple-treatment studies), Outcome 2 Hospital admission or poor response to treatment.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome: 2 Hospital admission or poor response to treatment

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adults					
Colacone 1993	1/40	0/40		1.5 %	3.00 [0.13, 71.51]
Dhuper 2008	1/29	2/29		6.1 %	0.50 [0.05, 5.21]
Idris 1993	1/15	1/20		2.6 %	1.33 [0.09, 19.64]
Raimondi 1997	0/9	0/9			Not estimable
Rao 2002	0/25	1/25		4.6 %	0.33 [0.01, 7.81]
Rodrigo 1993	5/49	4/48		12.3 %	1.22 [0.35, 4.29]
Rodriguez 1999	14/36	17/33		54.0 %	0.75 [0.45, 1.28]
Turner 1988	4/27	5/26		15.5 %	0.77 [0.23, 2.56]
Vivek 2003	5/68	1/54		3.4 %	3.97 [0.48, 32.98]
Subtotal (95% CI)	**298**	**284**		**100.0 %**	**0.94 [0.61, 1.43]**
Total events: 31 (Holding Chamber), 31 (Nebuliser)					
Heterogeneity: Chi^2 = 3.99, df = 7 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 0.29 (P = 0.77)					
2 Children					
Batra 1997	7/30	6/30		8.5 %	1.17 [0.44, 3.06]
Chong-Neto 2005	0/20	0/10			Not estimable
Chou 1995	4/71	5/81		6.6 %	0.91 [0.25, 3.27]
Direkwatanachai 2008	19/68	16/77		21.2 %	1.34 [0.75, 2.40]
Jamalvi 2006	4/84	7/66		11.1 %	0.45 [0.14, 1.47]
Leversha 2000	10/30	18/30		25.4 %	0.56 [0.31, 1.00]
Ploin 2000	3/31	3/32		4.2 %	1.03 [0.23, 4.73]
Sannier 2007	6/39	3/40		4.2 %	2.05 [0.55, 7.63]
Valencia 1999	7/32	5/38		6.5 %	1.66 [0.58, 4.74]
Vazquez 1992	0/9	0/9			Not estimable
Williams 1996	2/42	2/18		4.0 %	0.43 [0.07, 2.81]
Yasmin 2012	8/25	6/25		8.5 %	1.33 [0.54, 3.29]



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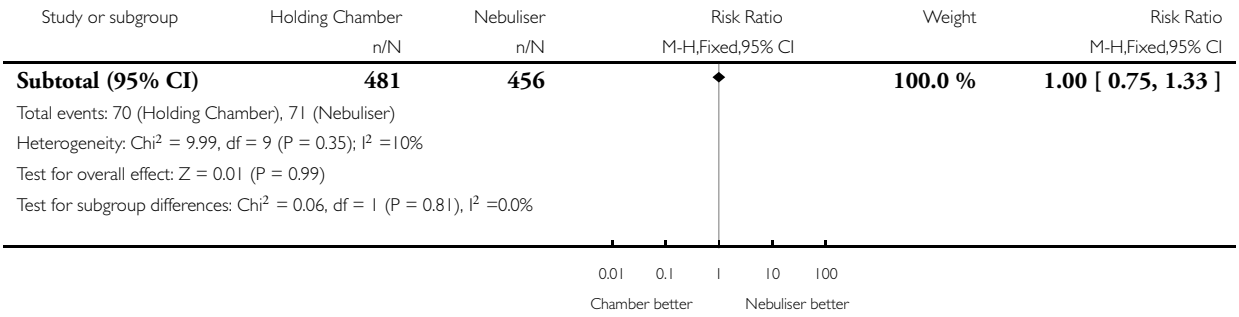
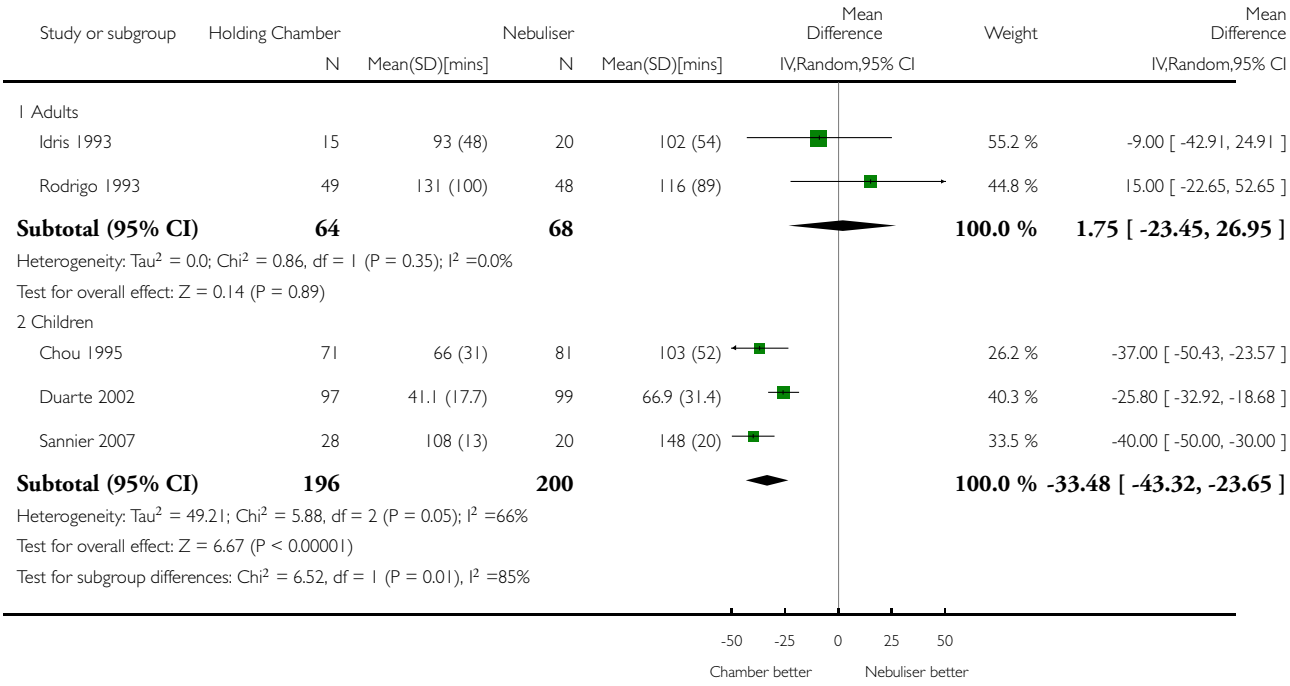


Analysis 1.3. Comparison 1 Spacer (chamber) versus nebuliser (multiple-treatment studies), Outcome 3 Duration in emergency department (minutes)..

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome: 3 Duration in emergency department (minutes).



Analysis 1.4. Comparison 1 Spacer (chamber) versus nebuliser (multiple-treatment studies), Outcome 4 Final rise in FEV_1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome: 4 Final rise in FEV_1 (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Colacone 1993	40	23 (16)	40	22 (19)		20.6 %	1.00 [-6.70, 8.70]
Idris 1993	15	27.1 (12.7)	20	26.4 (20.4)		10.1 %	0.70 [-10.31, 11.71]
Rao 2002	8	22.7 (14.21)	12	17.58 (13.18)		8.0 %	5.12 [-7.23, 17.47]
Rodrigo 1993	49	23 (15.6)	48	21.3 (12.7)		38.2 %	1.70 [-3.96, 7.36]
Rodrigo 1998	11	44.3 (16.7)	11	49.4 (21)		4.9 %	-5.10 [-20.96, 10.76]
Turner 1988	27	13.03 (13.88)	26	13.74 (16.41)		18.2 %	-0.71 [-8.91, 7.49]
Subtotal (95% CI)	**150**		**157**			**100.0 %**	**0.96 [-2.54, 4.46]**
Heterogeneity: Chi^2 = 1.22, df = 5 (P = 0.94); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
2 Children							
Chong-Neto 2005	20	34 (10)	10	34 (7)		90.7 %	0.0 [-6.17, 6.17]
Vazquez 1992	9	29.5 (23.4)	9	19.7 (17.8)		9.3 %	9.80 [-9.41, 29.01]
Subtotal (95% CI)	**29**		**19**			**100.0 %**	**0.92 [-4.96, 6.79]**
Heterogeneity: Chi^2 = 0.91, df = 1 (P = 0.34); I^2 =0.0%							
Test for overall effect: Z = 0.31 (P = 0.76)							
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.99), I^2 =0.0%							

Analysis 1.5. Comparison 1 Spacer (chamber) versus nebuliser (multiple-treatment studies), Outcome 5 30 minute rise in FEV1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome: 5 30 minute rise in FEV1 (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Rao 2002	25	19.56 (11.27)	25	15.6 (14.39)		17.3 %	3.96 [-3.20, 11.12]
Rodrigo 1993	49	17 (13.5)	48	15.5 (9.1)		42.6 %	1.50 [-3.07, 6.07]
Turner 1988	27	5.4 (7.5)	26	9.2 (9.8)		40.1 %	-3.80 [-8.51, 0.91]
Subtotal (95% CI)	**101**		**99**			**100.0 %**	**-0.20 [-3.18, 2.78]**

Heterogeneity: Chi^2 = 4.07, df = 2 (P = 0.13); I^2 =51%

Test for overall effect: Z = 0.13 (P = 0.90)

Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Spacer (chamber) versus nebuliser (multiple-treatment studies), Outcome 6 Severe asthmatics final rise in FEV1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome: 6 Severe asthmatics final rise in FEV1 (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Idris 1993	6	26 (20)	8	14 (18)		9.0 %	12.00 [-8.29, 32.29]
Raimondi 1997	9	29 (15)	9	27 (15)		19.3 %	2.00 [-11.86, 15.86]
Rodrigo 1993	19	22.6 (17.5)	20	19.7 (14.5)		36.2 %	2.90 [-7.21, 13.01]
Turner 1988	10	9.52 (11.01)	13	12.12 (14.02)		35.4 %	-2.60 [-12.83, 7.63]
Subtotal (95% CI)	**44**		**50**			**100.0 %**	**1.60 [-4.49, 7.69]**

Heterogeneity: Chi^2 = 1.72, df = 3 (P = 0.63); I^2 =0.0%

Test for overall effect: Z = 0.51 (P = 0.61)

Test for subgroup differences: Not applicable

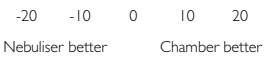
Analysis 1.7. Comparison 1 Spacer (chamber) versus nebuliser (multiple-treatment studies), Outcome 7 Final rise in peak flow (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome: 7 Final rise in peak flow (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Rao 2002	8	14.24 (15.56)	12	15.43 (9.69)		11.6 %	-1.19 [-13.29, 10.91]
Rodrigo 1993	49	22.1 (13)	48	21.4 (10)		79.7 %	0.70 [-3.91, 5.31]
Rodrigo 1998	11	47.5 (14.4)	11	57.9 (18.7)		8.7 %	-10.40 [-24.35, 3.55]
Subtotal (95% CI)	**68**		**71**			**100.0 %**	**-0.49 [-4.60, 3.63]**
Heterogeneity: Chi² = 2.21, df = 2 (P = 0.33); I² =9%							
Test for overall effect: Z = 0.23 (P = 0.82)							
2 Children							
Chou 1995	39	19 (19.5)	49	25 (19.1)		52.6 %	-6.00 [-14.13, 2.13]
Vazquez 1992	9	29.6 (21.4)	9	25.5 (19.5)		9.7 %	4.10 [-14.81, 23.01]
Williams 1996	42	25 (18.2)	18	25.61 (17)		37.7 %	-0.61 [-10.20, 8.98]
Subtotal (95% CI)	**90**		**76**			**100.0 %**	**-2.99 [-8.88, 2.91]**
Heterogeneity: Chi² = 1.30, df = 2 (P = 0.52); I² =0.0%							
Test for overall effect: Z = 0.99 (P = 0.32)							
Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² =0.0%							



Analysis 1.8. Comparison 1 Spacer (chamber) versus nebuliser (multiple-treatment studies), Outcome 8 30 minute rise in peak flow (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome: 8 30 minute rise in peak flow (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Rao 2002	25	14.24 (13.94)	25	12.52 (14.24)		21.2 %	1.72 [-6.09, 9.53]
Rodrigo 1993	49	15.4 (11.4)	48	14.7 (8.8)		78.8 %	0.70 [-3.35, 4.75]
Subtotal (95% CI)	**74**		**73**			**100.0 %**	**0.92 [-2.68, 4.51]**

Heterogeneity: $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 0.50 (P = 0.62)

Test for subgroup differences: Not applicable

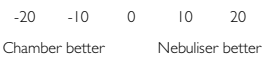
Analysis 1.9. Comparison 1 Spacer (chamber) versus nebuliser (multiple-treatment studies), Outcome 9 Rise in pulse rate (% baseline).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome: 9 Rise in pulse rate (% baseline)

Study or subgroup	Holding Chamber N	Mean(SD)[%]	Nebuliser N	Mean(SD)[%]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Adults							
Colacone 1993	40	-1 (19)	40	4 (19)		11.6 %	-5.00 [-13.33, 3.33]
Idris 1993	15	1 (16)	20	0 (18)		6.3 %	1.00 [-10.30, 12.30]
Rao 2002	8	-15.91 (6.95)	12	-12.58 (9.02)		16.3 %	-3.33 [-10.35, 3.69]
Rodrigo 1993	49	-1.32 (13.8)	48	-0.44 (14.2)		25.8 %	-0.88 [-6.45, 4.69]
Rodrigo 1998	11	-10 (19.7)	11	-2 (19.7)		3.0 %	-8.00 [-24.46, 8.46]
Rodriguez 1999	36	0 (11.7)	33	-1.3 (10.7)		28.7 %	1.30 [-3.99, 6.59]
Turner 1988	27	-4 (16)	26	-3 (20)		8.4 %	-1.00 [-10.77, 8.77]
Subtotal (95% CI)	**186**		**190**			**100.0 %**	**-1.23 [-4.06, 1.60]**
Heterogeneity: Tau² = 0.0; Chi² = 2.83, df = 6 (P = 0.83); I² =0.0%							
Test for overall effect: Z = 0.85 (P = 0.39)							
2 Children							
Batra 1997	30	-12.8 (9.4)	30	-7.4 (11.6)		13.0 %	-5.40 [-10.74, -0.06]
Chong-Neto 2005	20	20.6 (10.4)	10	32.9 (12.2)		7.4 %	-12.30 [-21.13, -3.47]
Chou 1995	71	5 (12.4)	81	15 (17.3)		14.2 %	-10.00 [-14.74, -5.26]
Duarte 2002	34	15 (20.7)	38	20 (18.1)		7.2 %	-5.00 [-14.03, 4.03]
Jamalvi 2006	84	-18 (16.4)	66	-17 (15.7)		13.3 %	-1.00 [-6.16, 4.16]
Leversha 2000	30	0.11 (7.2)	30	7.26 (7.2)		16.8 %	-7.15 [-10.79, -3.51]
Sannier 2007	39	22.8 (24.7)	39	20.2 (12.4)		7.6 %	2.60 [-6.07, 11.27]
Vazquez 1992	9	-10 (10)	9	0 (8)		8.0 %	-10.00 [-18.37, -1.63]
Yasmin 2012	25	-3 (9.1)	25	-2.4 (11)		12.4 %	-0.60 [-6.20, 5.00]
Subtotal (95% CI)	**342**		**328**			**100.0 %**	**-5.41 [-8.34, -2.48]**
Heterogeneity: Tau² = 9.86; Chi² = 16.85, df = 8 (P = 0.03); I² =53%							
Test for overall effect: Z = 3.61 (P = 0.00030)							
Test for subgroup differences: Chi² = 4.03, df = 1 (P = 0.04), I² =75%							



Analysis 1.10. Comparison 1 Spacer (chamber) versus nebuliser (multiple-treatment studies), Outcome 10 % Oxygen saturation (change from baseline).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome: 10 % Oxygen saturation (change from baseline)

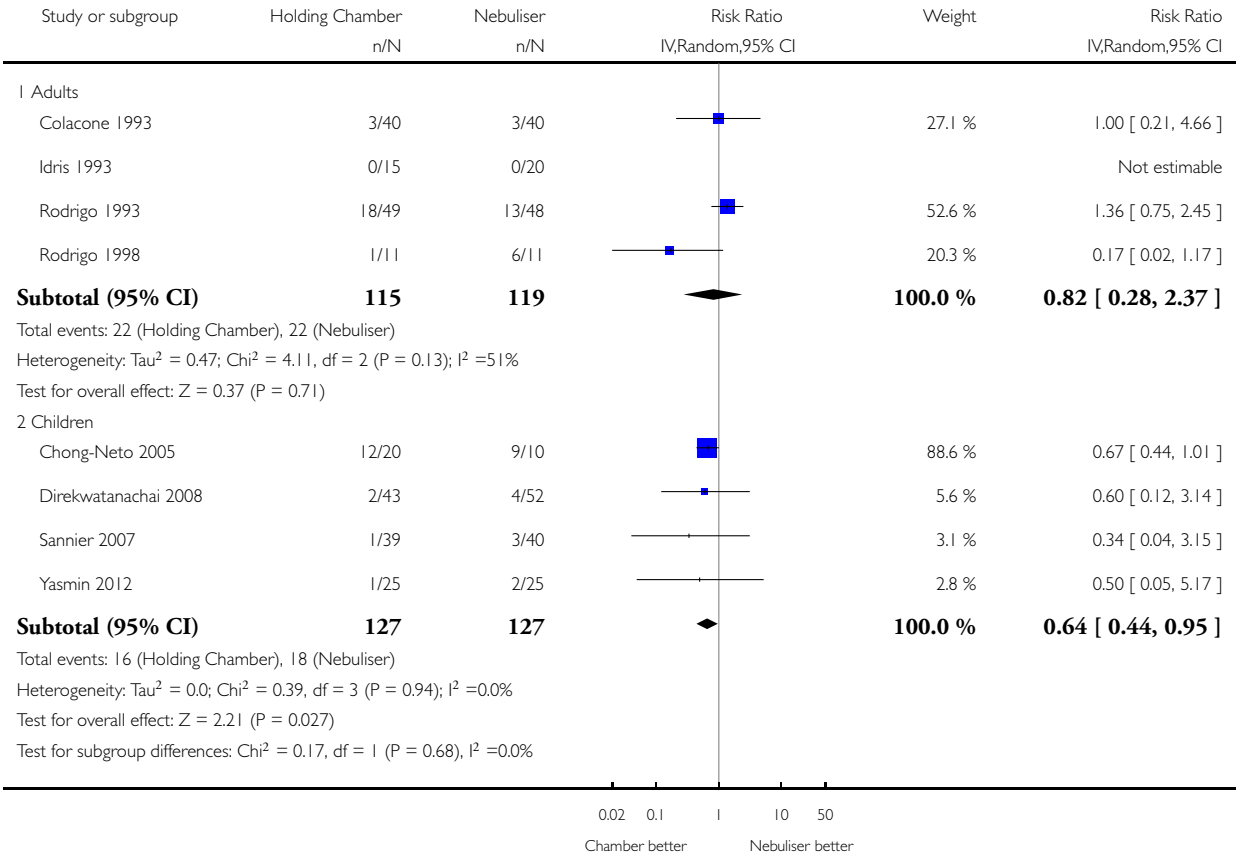
Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Children							
Direkwatanachai 2008	68	0.68 (2.07)	77	0.75 (1.94)		41.2 %	-0.07 [-0.73, 0.59]
Duarte 2002	34	1.5 (2.5)	38	1.2 (6.3)		3.8 %	0.30 [-1.87, 2.47]
Leversha 2000	30	0.67 (2.35)	30	1 (2.35)		12.5 %	-0.33 [-1.52, 0.86]
Sannier 2007	39	1.2 (1.5)	40	1.4 (2.1)		27.5 %	-0.20 [-1.00, 0.60]
Valencia 1999	32	1.71 (4.46)	38	1.45 (3.84)		4.6 %	0.26 [-1.71, 2.23]
Yasmin 2012	25	5.8 (1.8)	25	6.6 (2.8)		10.4 %	-0.80 [-2.10, 0.50]
Subtotal (95% CI)	**228**		**248**			**100.0 %**	**-0.19 [-0.61, 0.24]**
Heterogeneity: Chi^2 = 1.42, df = 5 (P = 0.92); I^2 =0.0%							
Test for overall effect: Z = 0.86 (P = 0.39)							
Test for subgroup differences: Not applicable							

Analysis 1.11. Comparison 1 Spacer (chamber) versus nebuliser (multiple-treatment studies), Outcome 11 Number of participants developing tremor.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome: 11 Number of participants developing tremor

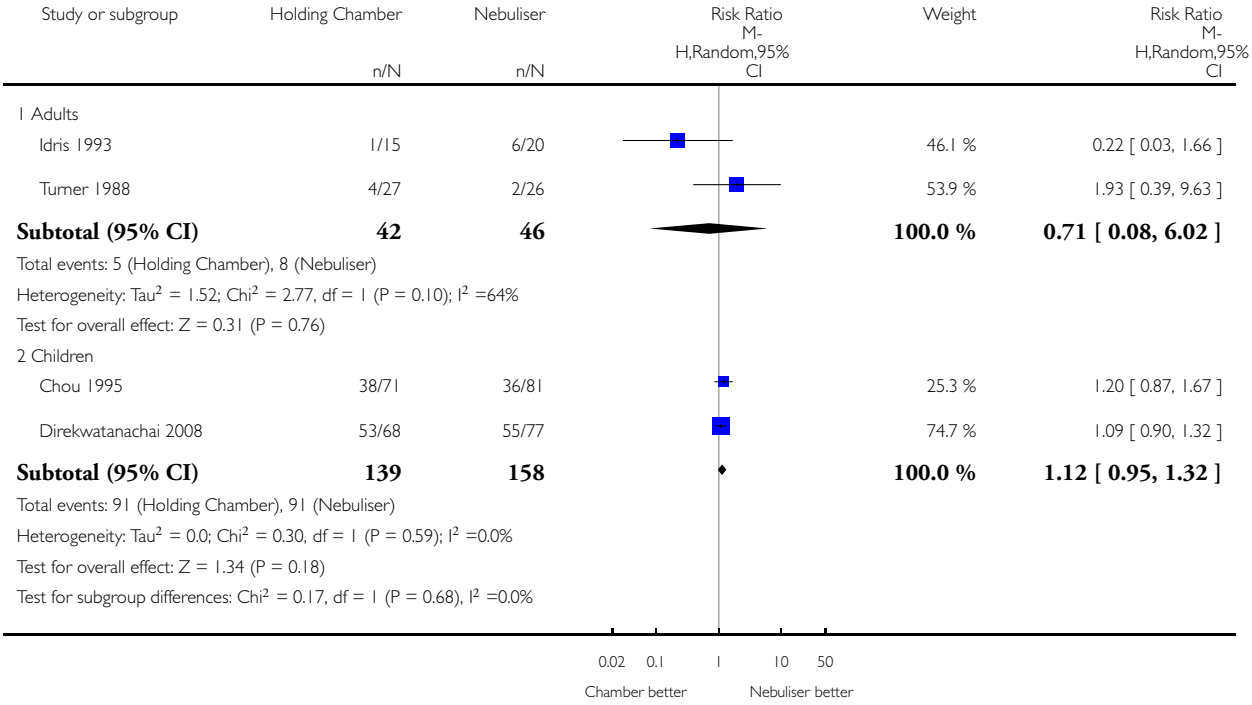


Analysis 1.12. Comparison 1 Spacer (chamber) versus nebuliser (multiple-treatment studies), Outcome 12 Number of participants given steroids.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome: 12 Number of participants given steroids



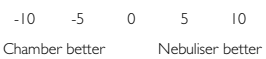
Analysis 1.13. Comparison 1 Spacer (chamber) versus nebuliser (multiple-treatment studies), Outcome 13 Rise in respiratory rate (breaths per minute).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus nebuliser (multiple-treatment studies)

Outcome: 13 Rise in respiratory rate (breaths per minute)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Adults							
Colacone 1993	40	-3 (6.3)	40	-3 (7.6)		19.6 %	0.0 [-3.06, 3.06]
Idris 1993	15	-5 (4)	20	-2 (6)		18.7 %	-3.00 [-6.32, 0.32]
Rao 2002	8	-8.62 (3.38)	12	-6.23 (3.39)		19.7 %	-2.39 [-5.42, 0.64]
Rodriguez 1999	36	-3.3 (5.5)	33	-6.5 (5.2)		21.5 %	3.20 [0.68, 5.72]
Turner 1988	27	-3 (5.2)	26	-6 (5.1)		20.6 %	3.00 [0.23, 5.77]
Subtotal (95% CI)	**126**		**131**			**100.0 %**	**0.28 [-2.29, 2.84]**
Heterogeneity: $Tau^2 = 6.29$; $Chi^2 = 15.37$, df = 4 (P = 0.004); $I^2 = 74\%$							
Test for overall effect: Z = 0.21 (P = 0.83)							
2 Children							
Batra 1997	30	-23.5 (6.7)	30	-20.9 (7.4)		12.3 %	-2.60 [-6.17, 0.97]
Direkwatanachai 2008	68	-4.84 (5.73)	77	-5.64 (5.38)		18.1 %	0.80 [-1.02, 2.62]
Duarte 2002	34	-6 (4.1)	38	-4 (5.9)		16.3 %	-2.00 [-4.33, 0.33]
Jamalvi 2006	84	-22 (9.2)	66	-19 (10.9)		13.1 %	-3.00 [-6.28, 0.28]
Leversha 2000	30	0.13 (8)	30	-1.21 (8)		10.9 %	1.34 [-2.71, 5.39]
Sannier 2007	39	-1.14 (9)	40	-5.05 (9.9)		10.6 %	3.91 [-0.26, 8.08]
Valencia 1999	32	-3.13 (16.4)	38	-4.07 (14.34)		5.2 %	0.94 [-6.35, 8.23]
Yasmin 2012	25	-24.5 (6.4)	25	-19.7 (4.9)		13.5 %	-4.80 [-7.96, -1.64]
Subtotal (95% CI)	**342**		**344**			**100.0 %**	**-0.94 [-2.84, 0.97]**
Heterogeneity: $Tau^2 = 4.35$; $Chi^2 = 19.04$, df = 7 (P = 0.01); $I^2 = 63\%$							
Test for overall effect: Z = 0.96 (P = 0.33)							



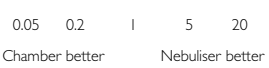
Analysis 2.1. Comparison 2 Spacer (chamber) versus nebuliser (single-treatment studies), Outcome 1 Hospital admission.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus nebuliser (single-treatment studies)

Outcome: 1 Hospital admission

Study or subgroup	Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adults				
Salzman 1989	6/24	3/20		1.67 [0.48, 5.83]
2 Children				
Ferr s 1989	2/41	4/48		0.59 [0.11, 3.03]
Freelander 1984	1/14	3/14		0.33 [0.04, 2.83]
Hussein 2002	3/30	4/30		0.75 [0.18, 3.07]
Kerem 1993	5/17	6/16		0.78 [0.30, 2.07]



Analysis 2.2. Comparison 2 Spacer (chamber) versus nebuliser (single-treatment studies), Outcome 2 Final peak flow (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus nebuliser (single-treatment studies)

Outcome: 2 Final peak flow (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
2 Children						
Ferr s 1989	41	68.8 (9.1)	48	64.9 (8.6)		3.90 [0.20, 7.60]

Analysis 2.3. Comparison 2 Spacer (chamber) versus nebuliser (single-treatment studies), Outcome 3 30 minute rise in FEV1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus nebuliser (single-treatment studies)

Outcome: 3 30 minute rise in FEV1 (% predicted)

Study or subgroup	Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
Salzman 1989	24	12.8 (13.2)	20	11 (15.2)		1.80 [-6.70, 10.30]
2 Children						
Kerem 1993	17	8 (10.15)	16	4.93 (9.12)		3.07 [-3.51, 9.65]

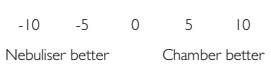
Analysis 2.4. Comparison 2 Spacer (chamber) versus nebuliser (single-treatment studies), Outcome 4 15 minute rise in FEV_1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus nebuliser (single-treatment studies)

Outcome: 4 15 minute rise in FEV_1 (% predicted)

Study or subgroup	Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Children						
Lin 1995	56	13.06 (13)	55	8.66 (9)		4.40 [0.25, 8.55]



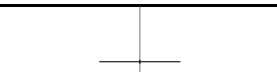
Analysis 2.5. Comparison 2 Spacer (chamber) versus nebuliser (single-treatment studies), Outcome 5 30 minute rise in peak flow (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus nebuliser (single-treatment studies)

Outcome: 5 30 minute rise in peak flow (% predicted)

Study or subgroup	Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
Morrone 1990	22	16 (13)	22	16 (13)		0.0 [-7.68, 7.68]
2 Children						
Freelander 1984	11	20 (27)	6	20 (25)		0.0 [-25.59, 25.59]
Robertson 1998	29	9 (22)	30	21 (33)		-12.00 [-26.27, 2.27]



Analysis 2.6. Comparison 2 Spacer (chamber) versus nebuliser (single-treatment studies), Outcome 6 15 minute rise in peak flow (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus nebuliser (single-treatment studies)

Outcome: 6 15 minute rise in peak flow (% predicted)

Study or subgroup	Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Children						
Lin 1995	56	12.54 (20)	55	2.49 (8)		10.05 [4.40, 15.70]

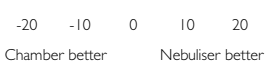
Analysis 2.7. Comparison 2 Spacer (chamber) versus nebuliser (single-treatment studies), Outcome 7 Rise in pulse rate (% baseline).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus nebuliser (single-treatment studies)

Outcome: 7 Rise in pulse rate (% baseline)

Study or subgroup	Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
Salzman 1989	24	-4 (20)	20	-8 (10)		4.00 [-5.12, 13.12]
2 Children						
Kerem 1993	17	-6.8 (14.4)	16	11.8 (27.4)		-18.60 [-33.67, -3.53]
Lin 1995	56	1 (17)	55	2 (19)		-1.00 [-7.71, 5.71]



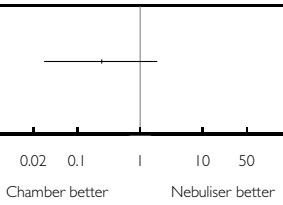
Analysis 2.8. Comparison 2 Spacer (chamber) versus nebuliser (single-treatment studies), Outcome 8 Number of participants developing tremor.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus nebuliser (single-treatment studies)

Outcome: 8 Number of participants developing tremor

Study or subgroup	Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Children				
Kerem 1993	1/17	4/16		0.24 [0.03, 1.89]



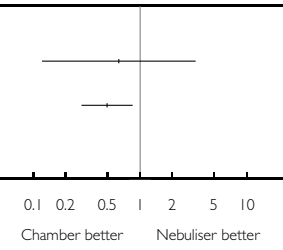
Analysis 2.9. Comparison 2 Spacer (chamber) versus nebuliser (single-treatment studies), Outcome 9 Number of participants with deterioration in blood gases.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus nebuliser (single-treatment studies)

Outcome: 9 Number of participants with deterioration in blood gases

Study or subgroup	Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Children				
Kerem 1993	2/17	3/16		0.63 [0.12, 3.28]
Lin 1995	13/56	26/55		0.49 [0.28, 0.85]



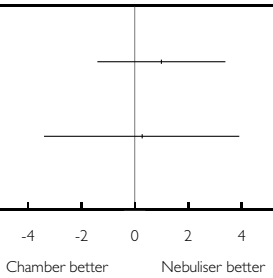
Analysis 2.10. Comparison 2 Spacer (chamber) versus nebuliser (single-treatment studies), Outcome 10 Rise in respiratory rate.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus nebuliser (single-treatment studies)

Outcome: 10 Rise in respiratory rate

Study or subgroup	Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
Salzman 1989	24	-3 (3.9)	20	-4 (4.2)		1.00 [-1.41, 3.41]
2 Children						
Kerem 1993	17	-4.06 (6.38)	16	-4.33 (4.17)		0.27 [-3.39, 3.93]

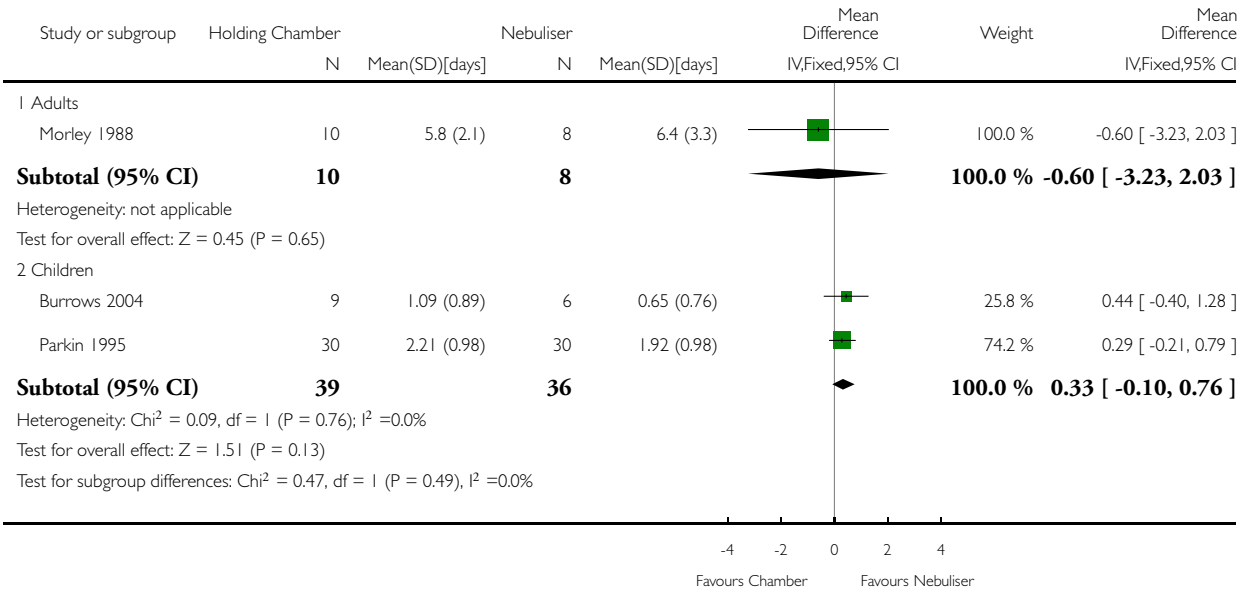


Analysis 3.1. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 1 Duration of hospital admission (days).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 1 Duration of hospital admission (days)



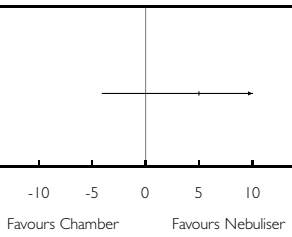
Analysis 3.2. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 2 Number of hours until reached 4-hourly dosing regimen.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 2 Number of hours until reached 4-hourly dosing regimen

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
2 Children						
Parkin 1995	30	24 (18.07)	30	19 (18.07)		5.00 [-4.14, 14.14]



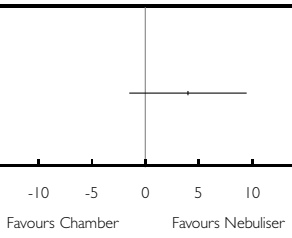
Analysis 3.3. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 3 Total number of inhaled doses received.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 3 Total number of inhaled doses received

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
2 Children						
Parkin 1995	30	21 (10.95)	30	17 (10.95)		4.00 [-1.54, 9.54]



Analysis 3.4. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 4 Number of participants returning to normal PEFR and respiratory score levels (end of study).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 4 Number of participants returning to normal PEFR and respiratory score levels (end of study)

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adults				
2 Children				
Coker 1995	7/12	10/12		0.70 [0.41, 1.20]

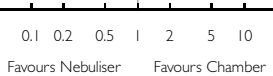
Analysis 3.5. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 5 Number of symptom-free participants 14 days post-discharge.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 5 Number of symptom-free participants 14 days post-discharge

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adults				
2 Children				
Parkin 1995	19/30	20/30		0.95 [0.66, 1.38]



Analysis 3.6. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 6 Readmissions in the subsequent 12 months.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 6 Readmissions in the subsequent 12 months

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adults				
2 Children				
Dewar 1999	4/29	9/33		0.51 [0.17, 1.47]

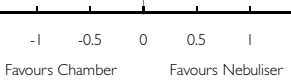
Analysis 3.7. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 7 Clinical asthma score (end of trial).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 7 Clinical asthma score (end of trial)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
2 Children						
Parkin 1995	30	2 (1.64)	30	2.2 (1.64)		-0.20 [-1.03, 0.63]

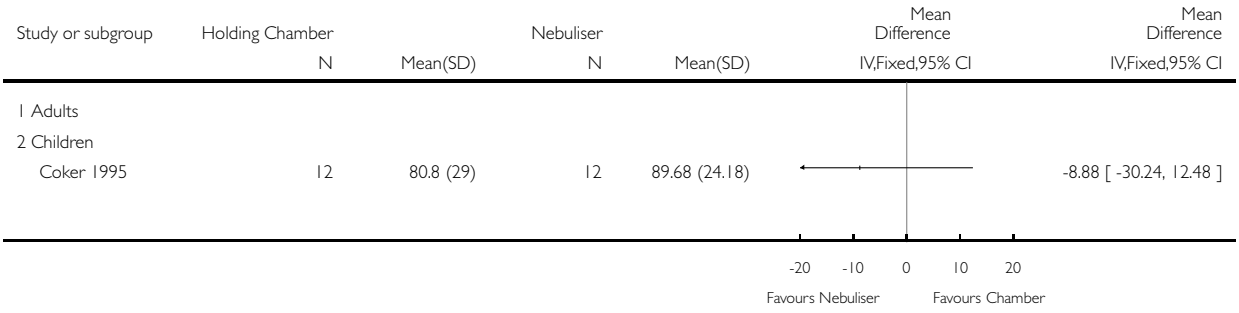


Analysis 3.8. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 8 Maximum percentage decrease in respiratory score.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 8 Maximum percentage decrease in respiratory score

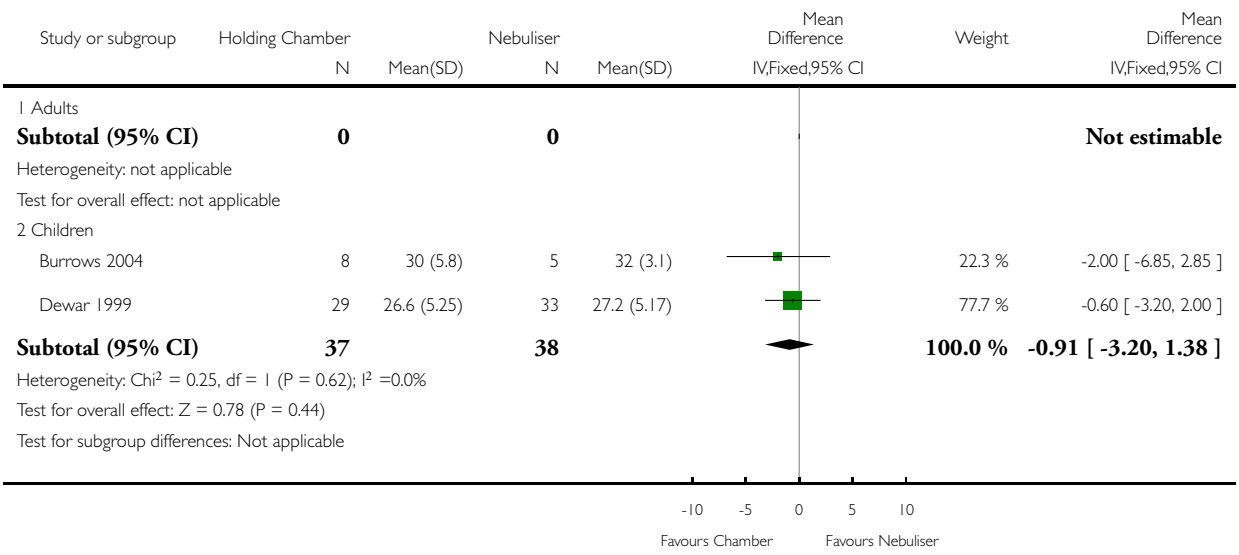


Analysis 3.9. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 9 Respiratory rate at discharge.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 9 Respiratory rate at discharge



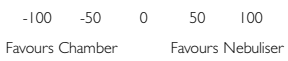
Analysis 3.10. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 10 Heart rate at discharge.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 10 Heart rate at discharge

Study or subgroup	Holding Chamber		Nebuliser		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Adults							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Children							
Burrows 2004	9	125 (27)	5	133 (16)		8.4 %	-8.00 [-30.54, 14.54]
Dewar 1999	29	101.2 (12.39)	33	99.3 (15.08)		91.6 %	1.90 [-4.94, 8.74]
Subtotal (95% CI)	**38**		**38**			**100.0 %**	**1.06 [-5.48, 7.61]**
Heterogeneity: Chi^2 = 0.68, df = 1 (P = 0.41); I^2 =0.0%							
Test for overall effect: Z = 0.32 (P = 0.75)							



Analysis 3.11. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 11 Oxygen saturations at discharge.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 11 Oxygen saturations at discharge

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Children							
Burrows 2004	9	95.5 (1.4)	5	96.8 (1.5)		11.3 %	-1.30 [-2.90, 0.30]
Dewar 1999	29	96.4 (1.35)	33	96.1 (0.86)		88.7 %	0.30 [-0.27, 0.87]
Subtotal (95% CI)	**38**		**38**			**100.0 %**	**0.12 [-0.42, 0.66]**
Heterogeneity: Chi^2 = 3.40, df = 1 (P = 0.07); I^2 =71%							
Test for overall effect: Z = 0.43 (P = 0.67)							

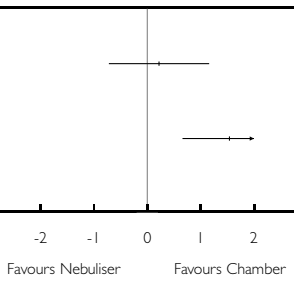
Analysis 3.12. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 12 30 minute rise in FEV1 .

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 12 30 minute rise in FEV1

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
1 Adults						
Morley 1988	10	1.92 (0.78)	8	1.72 (1)		0.22 [-0.72, 1.15]
2 Children						
Ba 1989	14	34.5 (9)	13	23.5 (3.5)		1.54 [0.66, 2.42]



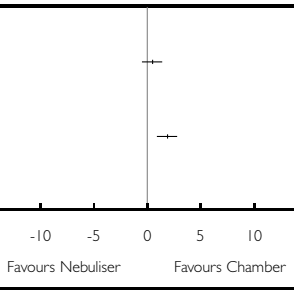
Analysis 3.13. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 13 Final rise in FEV1 .

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 13 Final rise in FEV1

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
1 Adults						
Morley 1988	10	1.87 (0.96)	8	1.46 (0.64)		0.47 [-0.48, 1.41]
2 Children						
Ba 1989	14	26 (9)	13	11.5 (5.5)		1.87 [0.94, 2.80]



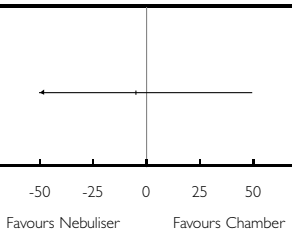
Analysis 3.14. Comparison 3 Spacer (chamber) versus nebuliser (inpatient studies), Outcome 14 Final rise in peak flow (% change from baseline).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus nebuliser (inpatient studies)

Outcome: 14 Final rise in peak flow (% change from baseline)

Study or subgroup	Holding Chamber		Nebuliser		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
1 Adults						
2 Children						
Coker 1995	12	100.62 (79.55)	12	105.43 (53.79)		-4.81 [-59.14, 49.52]

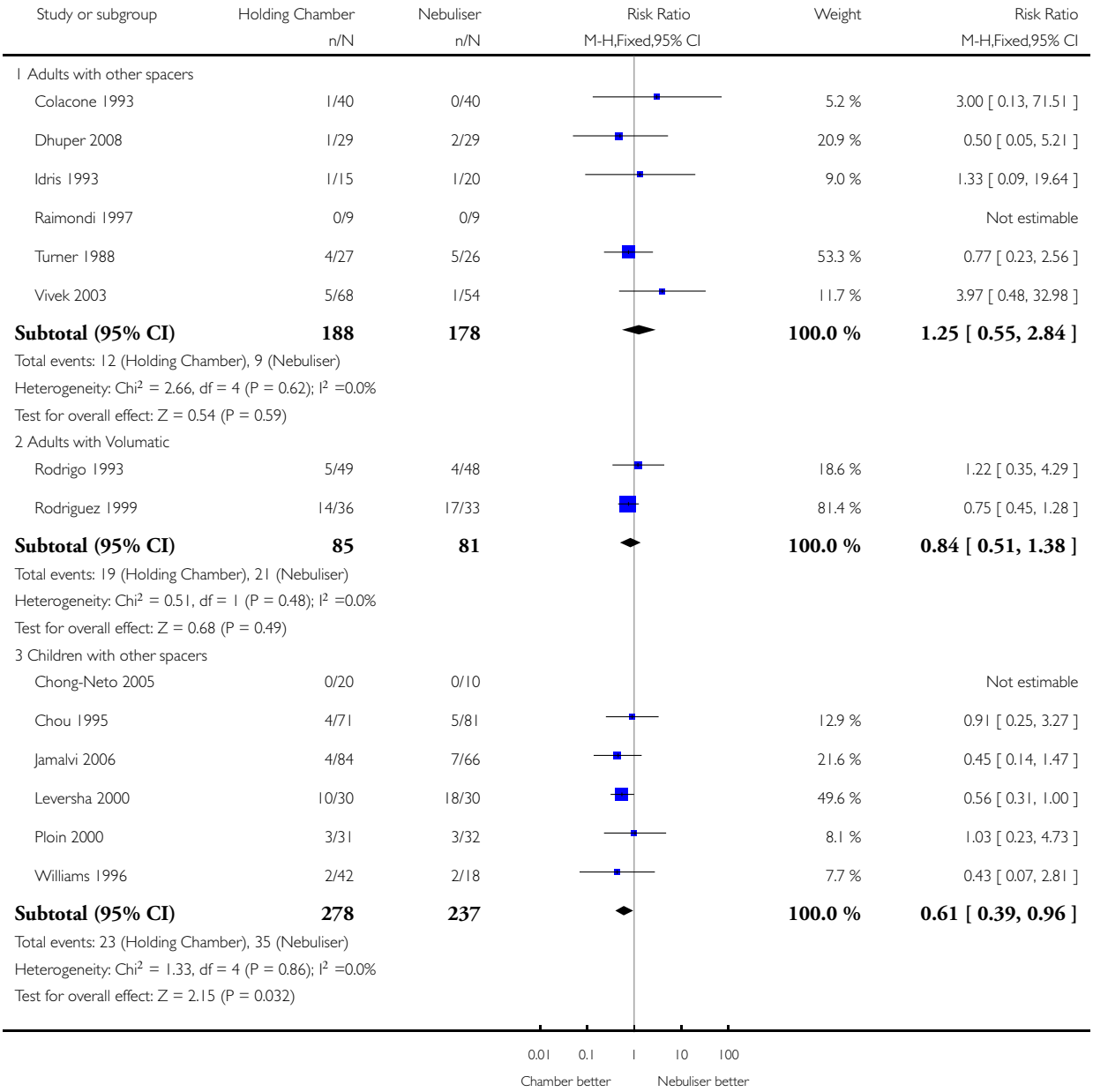


Analysis 4.1. Comparison 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups), Outcome 1 Hospital admission.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups)

Outcome: 1 Hospital admission



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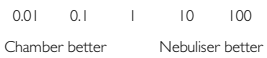
Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
4 Children with Volumatic					
Direkwatanachai 2008	1/68	2/77		100.0 %	0.57 [0.05, 6.11]
Vazquez 1992	0/9	0/9			Not estimable
Subtotal (95% CI)	**77**	**86**		**100.0 %**	**0.57 [0.05, 6.11]**
Total events: 1 (Holding Chamber), 2 (Nebuliser)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.47 (P = 0.64)					
Test for subgroup differences: Chi² = 2.60, df = 3 (P = 0.46), I² =0.0%					



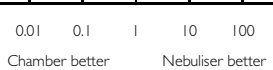
Analysis 4.2. Comparison 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups), Outcome 2 Hospital admission or poor response to treatment.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups)

Outcome: 2 Hospital admission or poor response to treatment

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adults with other spacers					
Colacone 1993	1/40	0/40		5.2 %	3.00 [0.13, 71.51]
Dhuper 2008	1/29	2/29		20.9 %	0.50 [0.05, 5.21]
Idris 1993	1/15	1/20		9.0 %	1.33 [0.09, 19.64]
Raimondi 1997	0/9	0/9			Not estimable
Turner 1988	4/27	5/26		53.3 %	0.77 [0.23, 2.56]
Vivek 2003	5/68	1/54		11.7 %	3.97 [0.48, 32.98]
Subtotal (95% CI)	**188**	**178**		**100.0 %**	**1.25 [0.55, 2.84]**
Total events: 12 (Holding Chamber), 9 (Nebuliser)					
Heterogeneity: Chi² = 2.66, df = 4 (P = 0.62); I² =0.0%					



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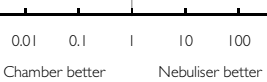
Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.54 (P = 0.59)					
2 Adults with Volumatic					
Rodrigo 1993	5/49	4/48		18.6 %	1.22 [0.35, 4.29]
Rodriguez 1999	14/36	17/33		81.4 %	0.75 [0.45, 1.28]
Subtotal (95% CI)	**85**	**81**		**100.0 %**	**0.84 [0.51, 1.38]**
Total events: 19 (Holding Chamber), 21 (Nebuliser)					
Heterogeneity: Chi^2 = 0.51, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 0.68 (P = 0.49)					
3 Children with other spacers					
Chong-Neto 2005	0/20	0/10			Not estimable
Chou 1995	4/71	5/81		10.0 %	0.91 [0.25, 3.27]
Jamalvi 2006	4/84	7/66		16.7 %	0.45 [0.14, 1.47]
Leversha 2000	10/30	18/30		38.4 %	0.56 [0.31, 1.00]
Ploin 2000	3/31	3/32		6.3 %	1.03 [0.23, 4.73]
Valencia 1999	7/32	5/38		9.8 %	1.66 [0.58, 4.74]
Williams 1996	2/42	2/18		6.0 %	0.43 [0.07, 2.81]
Yasmin 2012	8/25	6/25		12.8 %	1.33 [0.54, 3.29]
Subtotal (95% CI)	**335**	**300**		**100.0 %**	**0.80 [0.55, 1.16]**
Total events: 38 (Holding Chamber), 46 (Nebuliser)					
Heterogeneity: Chi^2 = 6.09, df = 6 (P = 0.41); I^2 =2%					
Test for overall effect: Z = 1.16 (P = 0.25)					
4 Children with Volumatic					
Batra 1997	7/30	6/30		28.6 %	1.17 [0.44, 3.06]
Direkwatanachai 2008	19/68	16/77		71.4 %	1.34 [0.75, 2.40]
Vazquez 1992	0/9	0/9			Not estimable
Subtotal (95% CI)	**107**	**116**		**100.0 %**	**1.29 [0.79, 2.13]**
Total events: 26 (Holding Chamber), 22 (Nebuliser)					
Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.80); I^2 =0.0%					
Test for overall effect: Z = 1.02 (P = 0.31)					
Test for subgroup differences: Chi^2 = 2.94, df = 3 (P = 0.40), I^2 =0.0%					

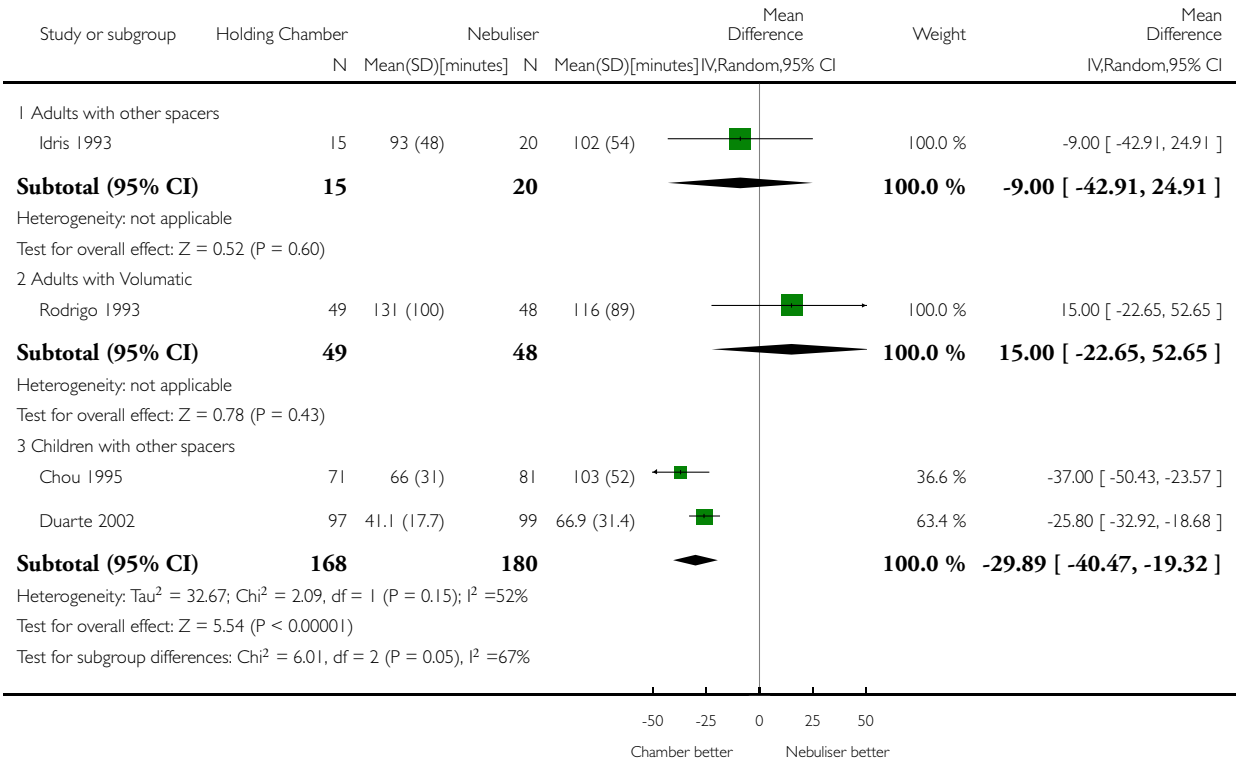


Analysis 4.3. Comparison 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups), Outcome 3 Duration in emergency department (minutes)..

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups)

Outcome: 3 Duration in emergency department (minutes).

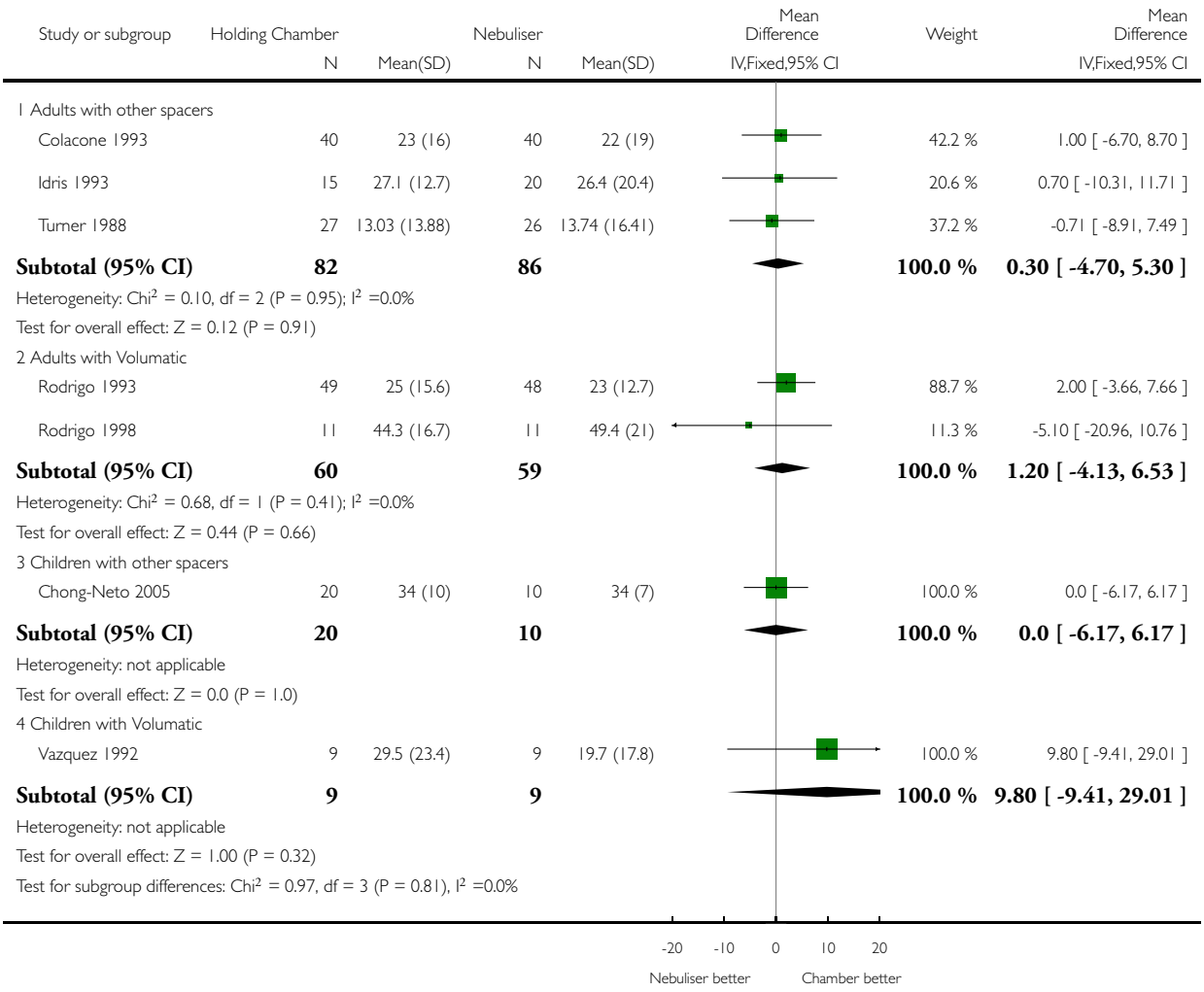


Analysis 4.4. Comparison 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups), Outcome 4 Final rise in FEV_1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups)

Outcome: 4 Final rise in FEV_1 (% predicted)



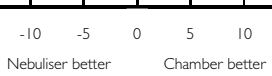
Analysis 4.5. Comparison 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups), Outcome 5 30 minute rise in FEV_1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups)

Outcome: 5 30 minute rise in FEV_1 (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults with other spacers							
Turner 1988	27	5.4 (7.5)	26	9.2 (9.8)		100.0 %	-3.80 [-8.51, 0.91]
Subtotal (95% CI)	**27**		**26**			**100.0 %**	**-3.80 [-8.51, 0.91]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.58 (P = 0.11)							
2 Adults with Volumatic							
Rodrigo 1993	49	17 (13.5)	48	15.5 (9.1)		100.0 %	1.50 [-3.07, 6.07]
Subtotal (95% CI)	**49**		**48**			**100.0 %**	**1.50 [-3.07, 6.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.64 (P = 0.52)							
Test for subgroup differences: Chi^2 = 2.50, df = 1 (P = 0.11), I^2 =60%							

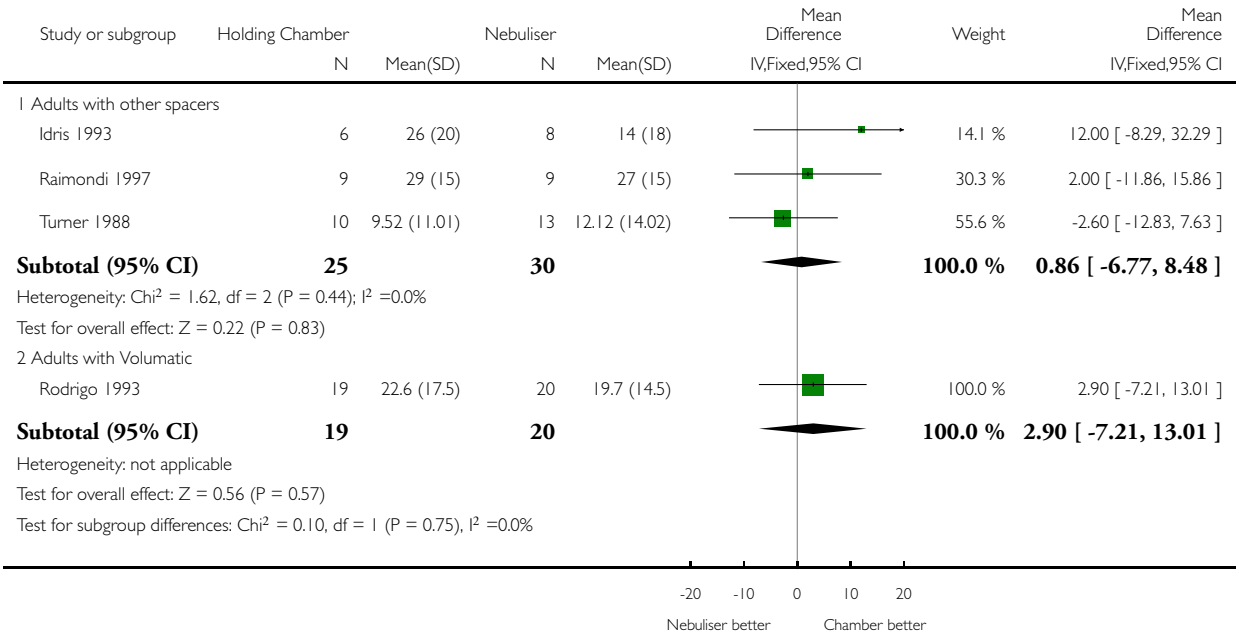


Analysis 4.6. Comparison 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups), Outcome 6 Severe asthmatics final rise in FEV1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups)

Outcome: 6 Severe asthmatics final rise in FEV1 (% predicted)

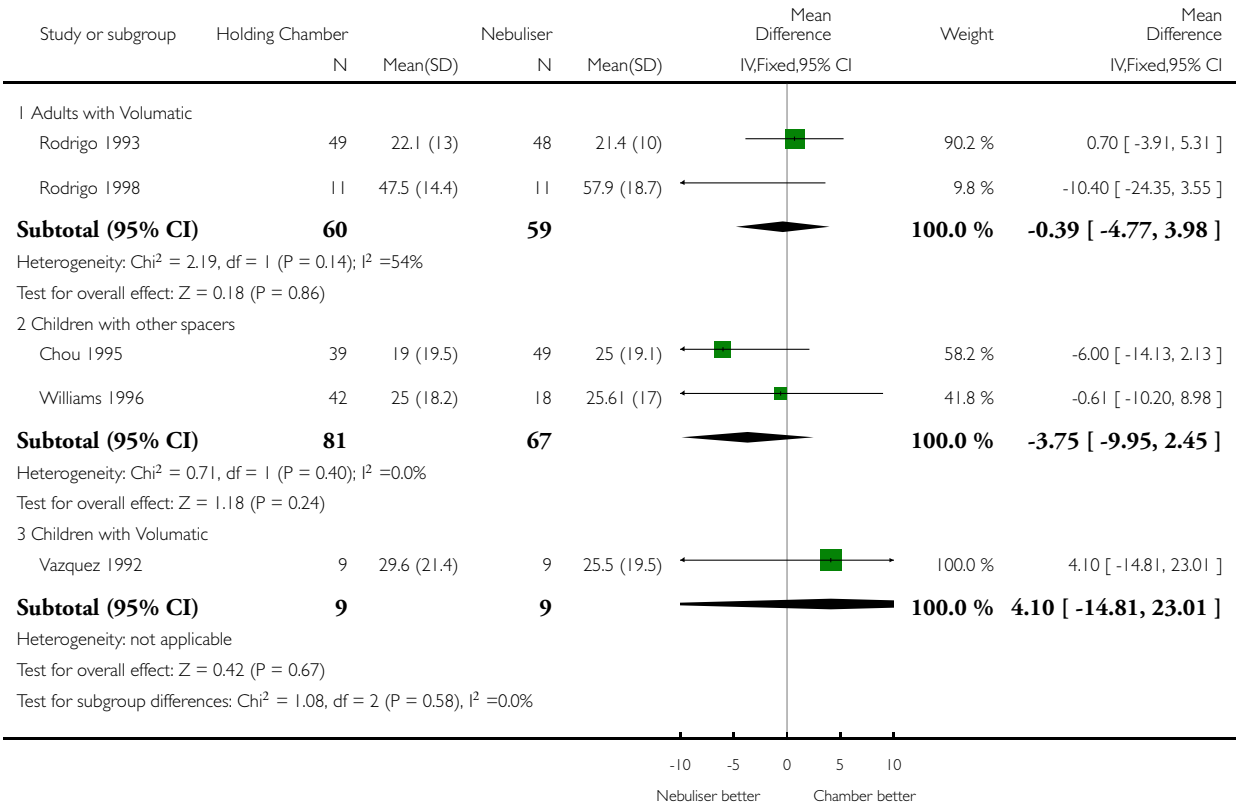


Analysis 4.7. Comparison 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups), Outcome 7 Final rise in peak flow (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups)

Outcome: 7 Final rise in peak flow (% predicted)



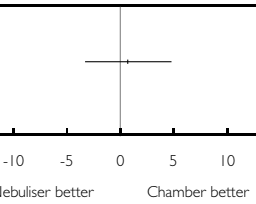
Analysis 4.8. Comparison 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups), Outcome 8 30 minute rise in peak flow (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups)

Outcome: 8 30 minute rise in peak flow (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults with Volumatic						
Rodrigo 1993	49	15.4 (11.4)	48	14.7 (8.8)		0.70 [-3.35, 4.75]

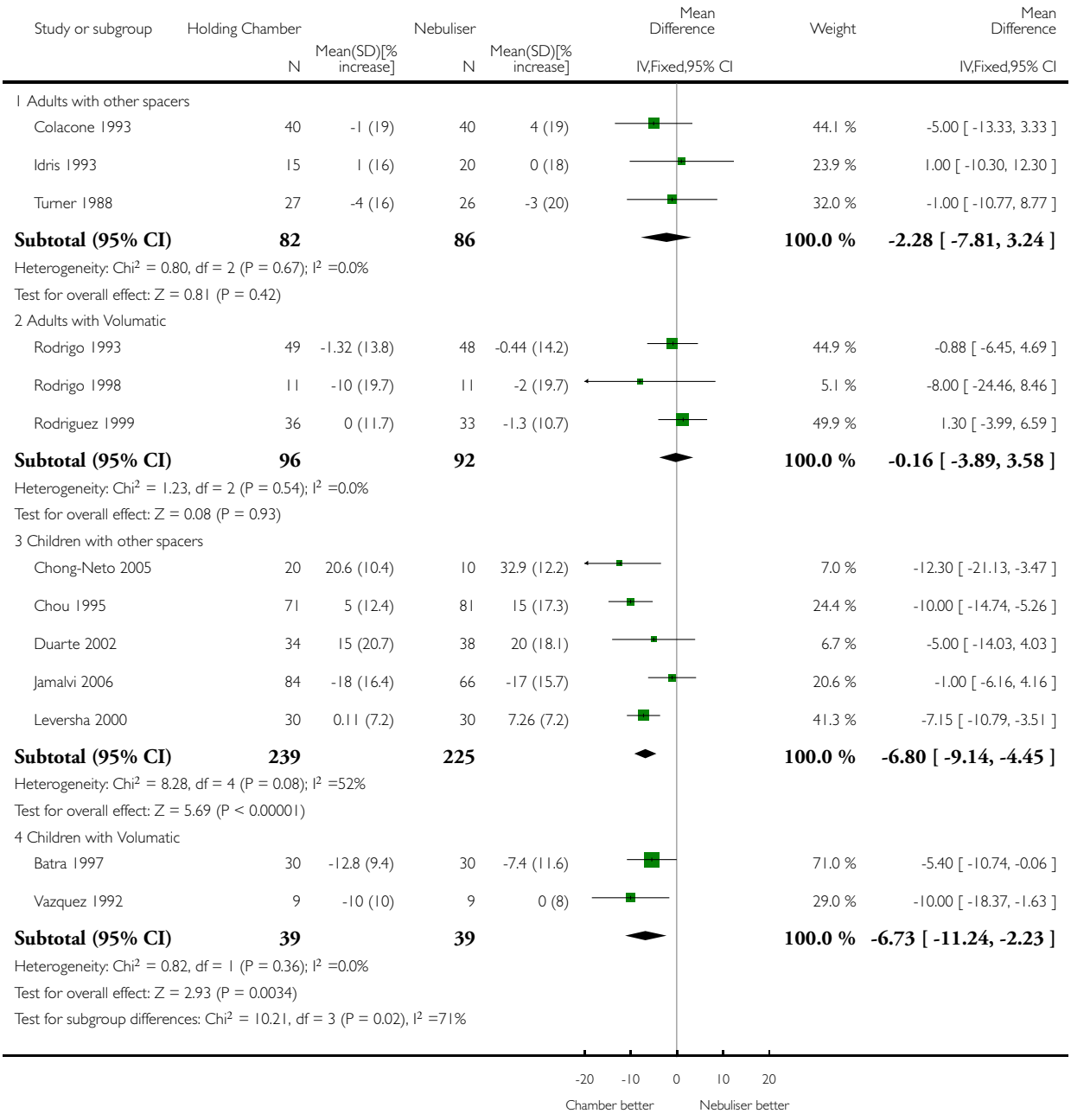


Analysis 4.9. Comparison 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups), Outcome 9 Rise in pulse rate (% baseline).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus nebuliser (multiple-treatment studies with Volumatic subgroups)

Outcome: 9 Rise in pulse rate (% baseline)



ADDITIONAL TABLES

Table 1. Details of spacers, design and location

Study ID	Spacer Type	Spacer Volume (mL)	Adults of Children	Number of subjects	Multiple or Single Treatments	Location	Study design
Ba 1989	Nebuhaler	750	Children	27	Multiple	Inpatients	Double dummy
Batra 1997	Volumatic	750	Children	60	Multiple	Casualty	Open
Burrows 2004	Volumatic	750	Children	29	Multiple	Inpatients	Open
Chong-Neto 2005	Aerochamber and home-made	145 or 500	Children	30	Multiple	Community	Dummy dry powder given to spacer group
Chou 1995	Aerochamber	145	Children	152	Multiple	Casualty	Open
Coker 1995	Volumatic	750	Children	24	Multiple	Inpatients	Open
Colacone 1993	Aerochamber	145	Adults	80	Multiple	Casualty	Double-dummy
Dewar 1999	Volumatic	750	Children	62	Multiple	Inpatients	Open
Dhuper 2008	Lite Aire	160	Adults	58	Multiple	Casualty	Double-dummy
Direk-watanachai 2008	Volumatic	750	Children	145	Multiple	Casualty & Outpatient Clinic	Open
Duarte 2002	home-made	500	Children	196	Multiple	Casualty	Open
Ferrés 1989	unknown	750	Children	100	Single	Casualty	Open
Freelander 1984	Nebuhaler	750	Children	28	Single	Casualty	Open
Hussein 2002	"Large volume"	NS	Children	60	Single	Casualty	Open
Idris 1993	Inspirease	650	Adults	35	Multiple	Casualty	Double-dummy
Jamalvi 2006	Babyhaler	350	Children	150	Multiple	Casualty	Open

Table 1. Details of spacers, design and location (*Continued*)

Kerem 1993	Volumatic	750	Children	33	Single	Casualty	Double-dummy
Leversha 2000	Aerochamber	145	Children	60	Multiple	Casualty	Double dummy
Lin 1995	Aerochamber	145	Children	111	Single	Casualty	Open
Maldano 1997	unknown	NS	Children	42	Multiple	Casualty	Open
Morley 1988	Inspirease	650	Adults	28	Multiple	Inpatients	Open
Morrone 1990	unknown	500	Adults	44	Single	Community	Open
Parkin 1995	Aerochamber	145	Children	65	Multiple	Inpatients	Open
Pendergast 1989	Nebuhaler	750	Children	27	Multiple	Casualty	Open
Ploin 2000	Babyhaler	350	Children	64	Multiple	Casualty	Double-dummy
Raimondi 1997	Aerochamber	145	Adults	27	Multiple	Casualty	Open
Rao 2002	unknown	NS	Adults	50	Multiple	Casualty	Double-dummy
Robertson 1998	Volumatic	750	Children	155	Single	Casualty	Double-dummy
Rodrigo 1993	Volumatic	750	Adults	97	Multiple	Casualty	Double-dummy
Rogrigo 1998	Volumatic	750	Adults	22	Multiple	Casualty	Double-dummy
Rodriguez 1999	Volumatic	750	Adults	69	Multiple	Casualty	Open
Salzman 1989	Aerochamber	145	Adults	44	Single	Casualty	Double-dummy
Sannier 2007	Varied according to child's home use	NS	Children	79	Multiple	Casualty	Open

Table 1. Details of spacers, design and location (*Continued*)

Turner 1988	Inspirease	650	Adults	53	Multiple	Casualty	Double-dummy
Valencia 1999	home-made	500	Children	70	Multiple	Casualty	Open
Vazquez 1992	Volumatic	750	Children	18	Multiple	Casualty	Open
Vivek 2003	Nebuhaler	750	Adults	122	Multiple	Casualty	Open
Williams 1996	Aerochamber	145	Children	60	Multiple	Casualty	Open
Yasmin 2012	Home-made spacer	250	Children	50	Multiple	Department of Paediatrics	Open

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*the Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Hand-searches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp “clinical trial [publication type]”/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.

5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11
The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

WHAT'S NEW

Last assessed as up-to-date: 14 February 2013.

Date	Event	Description
30 June 2014	Amended	The studies excluded life-threatening asthma, and this was added to the abstract

HISTORY

Protocol first published: Issue 2, 1996

Review first published: Issue 3, 1996

Date	Event	Description
9 May 2014	Amended	Amended a sentence in the conclusion to make it clearer that "in most cases nebulisers could be replaced with spacers to deliver beta -agonists in acute asthma" after receiving a suggestion from Andrés Infante Llanos. Thanks Andrés
4 November 2013	Amended	Typos corrected. Changed LABA to SABA in the discussion and expanded an occurence of LABA to beta$_2$-agonists.
14 February 2013	New search has been performed	Literature search run
14 February 2013	New citation required and conclusions have changed	Four further new studies including 58 adults and 295 children have been added (Dhuper 2008; Direkwatanachai 2008; Ferrés 1989 (single treatment) ; Yasmin 2012). Also individual patient data has been incorporated from Burrows 2004 for children over 2 years of age treated as inpatients. Two 'Summary of findings' Tables have been added. We also completed a new 'Risk of bias' assessment using the

(*Continued*)

		Review Manager 5 tool. Conclusions have been changed to emphasise the use of repeated treatments titrated to the participant's response in the trials
28 July 2008	New search has been performed	Converted to new review format and two new studies added (Jamalvi 2006 and Sannier 2007). No change in conclusions.
4 January 2006	New search has been performed	For the 2006 update of this review five new trials have been added: Burrows 2004 including 29 paediatric in-patients, Chong-Neto 2005 included 30 children given multiple treatments, Hussein 2002 including 60 children given a single treatment, Rao 2002 including 50 adults given multiple treatments and Vivek 2003 including 120 patients aged 10-50 (and therefore classified as adult) given multiple treatments. An additional table has been added with details of the holding chambers used in each study, and new comparisons added according to type of chamber. This was done because Volumatic spacers were no longer being manufactured (but they have now been reintroduced)
29 July 2003	New search has been performed	One trial was added to the review in 1997 (Williams 1996). Four further trials were added to the review in 1999 (Batra 1997; Maldano-Alanis 1997; Robertson 1998; Rodrigo 1998), but the conclusions of the review remained unchanged. For the 2001 update a further four studies were added (Leversha 2000; Ploin 2000; Rodriguez 1999; Valencia 1999) and reduced the confidence intervals around the results. One open trial in children has been added for the 2003 update (Duarte 2002) including a further 196 children studied in an emergency room setting in Brazil. In addition the 2003 update has expanded the review to include trials on in-patients and five new trials have been added including 184 children and 28 adults (Ba 1989, Coker 1995, Dewar 1999, Morley 1988 and Parkin 1995). The results of the in-patient trials are in keeping with the findings in the emergency room and community setting, that holding chambers can be as effective as nebulisers for delivery of beta-agonists in acute asthma

CONTRIBUTIONS OF AUTHORS

CJC had the initial idea for the review and wrote the protocol and review in conjunction with BHR. The data extraction and analysis were performed by CJC and the methodological quality was independently assessed by Robert Chapman for the original papers. Anna Bara independently assessed trials for inclusion, and extracted trial data for the 1997,1999 and 2001 updates. JAC and CJC assessed trials for inclusion and extracted data for the 2003 and 2006 update (to include trials on inpatients). CJC and BHR have updated the review to include further trials in 1997, 1999 and 2001. CJC, JAC and BHR have carried out the 2003, 2006, 2008 updates, and CJC and BHR carried out the 2013 update with help from William Griffiths, who independently assessed risks of bias and outcome data. EJW drafted the summary of findings table, contributed to discussion during the 2013 update and commented critically on the paper.

DECLARATIONS OF INTEREST

The authors have no financial interest in any of the devices used to deliver beta^2 -agonists in acute asthma and no involvement with the primary studies.

SOURCES OF SUPPORT

Internal sources

- NHS Executive, North Thames, UK.
- NHS Executive Eastern Region, UK.
- Department of Emergency Medicine, University of Alberta, Edmonton, Canada.
- St George's University of London, UK.

External sources

- Garfield Weston Foundation, UK.
- Canadian Institutes of Health Research (CIHR), Ottawa, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have now included studies on people who had been admitted to hospital, and we have used the Review Manager 5 'Risk of bias' tool and I^2 statistics (which were not available when the original protocol was written).

INDEX TERMS

Medical Subject Headings (MeSH)

*Nebulizers and Vaporizers; Acute Disease; Adrenergic beta-Agonists [*administration & dosage]; Anti-Asthmatic Agents [*administration & dosage]; Asthma [*drug therapy]; Emergency Service, Hospital [statistics & numerical data]; Equipment Design; Inhalation Spacers [statistics & numerical data]; Length of Stay [statistics & numerical data]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Child, Preschool; Humans