Review: Evidence of safety and efficacy of oral salbutamol preparations in the management of the wheezy child with acute respiratory infection and their role in the therapy of asthma in adults

REPORT

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INTRODUCTION

PROBLEM STATEMENT AND BACKGROUND:

Salbutamol is a β2 selective adrenoceptor and used in the treatment of bronchial asthma, both in children and adults extensively (1). It is also used, although, without evidence on efficacy, in the treatment of bronchitis (2) and bronchiolitis (3) as the clinical presentation of these conditions resemble that of bronchial asthma. Hence, evidence of safety and efficacy of salbutamol in the latter two conditions needs to be reviewed.

The efficacy and safety of salbutamol in the treatment and prophylaxis of asthma is well documented. However, the question is about the efficacy and safety of oral salbutamol preparations in the treatment and prophylaxis of asthma. Hence, its role in the therapy of adults (and children) with asthma also needs to be reviewed.

Components in this review:

As requested by the WHO EML Secretariat, this review on oral salbutamol preparations focuses on three aspects:

1. Evidence of their safety and efficacy in the management of the wheezy child with acute respiratory tract infections- It is an update of what has been already presented at the second meeting of the sub committee of the Expert Committee on the Selection and Use of Essential Medicines in 2008 by one of the reviewer who reviewed the document titled “Should oral salbutamol remain on the WHO Pediatric Model List?”
   a. Recommendation in the review: Oral dosage form to remain the Model List
   b. Recommendation by Reviewer 1: Agreed with the review and proposed the oral salbutamol not be removed from the Model List at present
   c. Recommendation by Reviewer 2: To delete both the oral liquid oral solid dosage forms of salbutamol from the Model EML

2. Describing the role of oral salbutamol in the therapy of adults with asthma – This is to find out whether oral salbutamol is recommended in treatment protocols.

3. Information about price and availability in resource poor settings – It is to find out availability and price of salbutamol preparations in resource poor settings. Data on both dosage forms are required.
**Indications for salbutamol:**

   - For the treatment and prophylaxis of asthma and other conditions associated with reversible airways obstruction.
   - Prophylaxis and treatment of asthma
   - Asthma, and other conditions associated with reversible airways obstruction, (and premature labour)
   - Acute asthma, exacerbation of reversible airway obstruction (including nocturnal asthma, and prevention of allergen or exercise induced bronchospasm) - *(Dose for oral dosage form is given, but says “but not recommended”)*

**Dosage forms of salbutamol:**

Salbutamol is available as Injection: 50 micrograms (as sulfate)/ml in 5 ml ampoule Metered dose inhaler (aerosol): 100 micrograms (as sulfate) per dose, Oral liquid: 0.4 mg/ml, Respirator solution for use in nebulizers: 5 mg (as sulfate)/ml and Tablet: 2 mg; 4 mg (as sulfate) (5).

Rational use of a medicine is not limited to selecting the most appropriate drug for a particular condition, but also includes selection of correct dose, suitable dosage forms and appropriate route of administration. Though both inhaled and oral salbutamol have demonstrated considerable bronchodilator effects, inhaled dosage forms have shown additional benefits. Salbutamol, as a bronchodilator needs to be delivered to the bronchi as quickly as possible preferably with minimal systemic side effects. The inhaled route (1) offers direct delivery to affected tissues, (2) has a quicker onset of action. (3) is effective in smaller doses than oral salbutamol and (4) causes fewer side effects.

The review submitted for the consideration of Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines in 2008 pointed out that over the last 20 years numerous asthma management reports have recommended inhaled salbutamol as the preferred mode of delivery (8). The review also pointed out that the “2007 Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma” exclusively discussed inhaled salbutamol for short-term asthma relief and made no mention of indications for use of the oral form (9).
Oral salbutamol remains a popular medicine. Despite recommendations discouraging oral β2-agonist use in children (10, 11), there appears to be widespread, regular use of this medication. In a survey of children enrolled in subsidized childcare and Head Start programs in East and Central Harlem, the authors found that oral β2-agonist was administered to 62% of children with persistent asthma (12).

But the reasons for oral salbutamol remaining as a popular medicine are not clear. It may be due to its efficacy and safety (in absolute terms, not in comparison with inhaled dosage forms), but moreover it may be due to some other socioeconomic reasons such as (1) non availability of inhaled dosage forms, (2) relatively high cost of inhaled dosage forms, (3) ease of using oral dosage form, (4) perceived social stigma in using inhalers, and (5) lack of time or resources to educate patients (and parents) about inhaler technique. Whether scientific bodies and evidence based formularies/guidelines should be influenced by these reasons have to be decided by the respective bodies and committees.

**Drug utilization studies:**

In Sri Lanka, we published a report on analysis of pharmaceuticals issued to the whole public sector over a period of 5 years (2002-2006) (13). Sri Lanka enjoys a free healthcare system where medicines are issued to patients free of charge. Findings related to salbutamol are given below. When the data on issues and money spent are compared, it is obvious that the unit price of the inhaled dosage forms is very much higher than that of oral dosage forms.

**Table 1: Issues of salbutamol (DDD/1000/Day) to public sector hospitals in Sri Lanka: 2002-2006**

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<thead>
<tr>
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<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
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<tbody>
<tr>
<td>Total</td>
<td>7.81</td>
<td>8.32</td>
<td>4.8</td>
<td>7.61</td>
<td>8.3</td>
</tr>
<tr>
<td>Non inhaled dosage forms of salbutamol (2, 4 mg tablets and 2 mg/5 ml syrup – a tiny proportion may be Parenteral)</td>
<td>7.76</td>
<td>8.01</td>
<td>4.46</td>
<td>6.99</td>
<td>7.02</td>
</tr>
<tr>
<td>Inhaled salbutamol (Includes respiratory solution as well)</td>
<td>0.05</td>
<td>0.31</td>
<td>0.24</td>
<td>0.62</td>
<td>1.28</td>
</tr>
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In all 5 years, salbutamol was within the top 11 issues (2002-6th, 2003-8th, 2004-111th, 2005-10th, 2006-10th).

The drop in 2004 not due to a real drop in issues, but a “pseudo” drop due to some administrative policy changes which have not been captured in the database.
Table 2: Money spent on issuing salbutamol (In Sri Lankan Million rupees) (1 Sri Lankan Million Rupees = 8772 USD)

<table>
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<tr>
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<tr>
<td>Total</td>
<td>19.51</td>
<td>25.40</td>
<td>20.81</td>
<td>36.78</td>
<td>46.48</td>
</tr>
<tr>
<td>Non inhaled dosage forms of salbutamol (2, 4 mg tablets and 2 mg/5 ml syrup – a tiny proportion may be Parenteral)</td>
<td>15</td>
<td>17.37</td>
<td>12</td>
<td>22.82</td>
<td>26.28</td>
</tr>
<tr>
<td>Inhaled salbutamol (Includes respiratory solution as well)</td>
<td>4.51</td>
<td>8.03</td>
<td>8.81</td>
<td>13.96</td>
<td>20.20</td>
</tr>
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We concluded “Our data on medicines issued for asthma are not in agreement with current evidence based treatment guidelines and needs urgent action to ensure accessibility to inhaled dosage forms”. We recommended that “it needs urgent action to ensure accessibility to inhaled dosage forms”. Though we have no documentary evidence for subsequent years (2007-2010), we know from various sources such as personal communications, observations and unpublished data on drug utilization and availability that our recommendation has not yet got into practice in Sri Lanka.

If we look from Sri Lankan policy makers and medical administrators point of view: In 2006, the proportion of inhaled and other dosage forms of salbutamol was 1: 5.5 in terms of DDD/1000/day as opposed to 1: 1.3 in terms of cost. This indicates the higher unit cost of inhaled dosage forms compared to other (mainly oral) dosage forms of salbutamol. This is the major obstacle in “ensuring accessibility to inhaled dosage forms” in the Public Sector in Sri Lanka.

**Purpose of essential medicines:**

Essential medicines are intended to be available within the context of functioning health systems at all times, in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford (14). If a community cannot afford to have the appropriate (inhaled) dosage forms in the EML, can it be allowed to have the alternative (oral) dosage form as well in the EML? So that one or other dosage form could be made available at all times, and in adequate amounts.
Other side of the argument:

A global advisory body such as the World Health Organization when developing the Model Essential Medicine List which will be used by many countries in developing their own national EMLs should base its recommendation only on scientific evidence on efficacy and safety of the product in the proposed indications. Do we have such evidence for oral salbutamol dosage forms?

RATIONALE FOR UNDERTAKING THE REVIEW:

Oral salbutamol is included in the WHO Model list in liquid and tablet formulation. However, discussions have been going on for a while whether these formulations should be in the list as “they are rarely used in the management of childhood asthma in many countries” (15). This prompted a need for a review of the evidence for the use of these forms, with particular emphasis on young children with viral-related wheeze. A review was subsequently received by the Secretariat and discussed in the second meeting of the subcommittee of the Expert Committee on the Selection and Use of Essential Medicine (2008). Expert comments from two reviewers were also received. Recommendations from the review and expert comments are given below (Extracted from Reference 14 and the 2008 documents sent by the Secretariat).

Review (8)

The recommendation was “Until much more is known about extent of usage of the oral form in multiple settings and the reasons why the community physicians are prescribing the oral form rather than the inhaled form, we suggest that both forms remain on the Model List of Essential Medicines for Children in appropriate dosage forms for children of all ages”. This recommendation was made despite the review “re-affirmed the present view of the superiority of inhaled vs. oral beta agonists for efficacy for treating asthma”. The review’s final recommendation to retain oral dosage form was based on:

- Extent of usage of oral salbutamol in multiple settings was not known
- Reasons for community physicians prescribing oral salbutamol were unknown
- Cost of inhaled dosage forms (especially the CFC free preparations) preventing their wider usage
- Lack of resources for education and training required for sustained use of inhaled dosage forms

Hence, oral salbutamol affords clinically significant bronchodilatation and should be considered a treatment option in cases where patients are unable to coordinate use of an inhaler/ compliance with inhaled dosage forms cannot be assured
Reviewer 1:
“In line with the recommendation of the review, the committee should not remove oral salbutamol from the Model List at present”.
The reviewer agreed that there is no adequate evidence of efficacy for the proposed use and there is no evidence of efficacy in diverse settings and/or populations. However, his/her recommendations were also based on claims similar to what have been stated in the review.
“The continued inclusion of oral Salbutamol is a vexed issue. Overall, the review demonstrates that inhaled Salbutamol is a superior treatment to oral Salbutamol and both are significantly superior to placebo. The unanswered question is the utility, acceptability and practicalities of the salbutamol inhaler (with a spacer device) in all situations where children would need access to salbutamol. The review offers anecdote that puffers are problematic in a developed country and, it is conceivable, that similar circumstances would occur in the developing world”.

Reviewer 2:
“Delete both the oral liquid (2 mg/5 ml oral liquid) and oral solid dosage forms (2 mg; 4 mg (as sulfate) tablets) of salbutamol from the Model EML (as listed in section 25.1 ‘Antiasthmatic and medicines for chronic obstructive pulmonary disease’)”
In addition to the evidence given in the review (mainly focusing bronchial asthma), the reviewer has looked into evidence for use of oral salbutamol “especially in young children with viral related wheeze”. The recommendation to delete the oral dosage form was based on:
• The agreement with the review that (1) the inhaled route offers direct delivery to affected tissues and has a quicker onset of action and (2) inhaled salbutamol is effective in smaller doses than oral salbutamol and causes fewer side effects.
• Three studies (16, 17, 18) concluding “no significant differences in the outcomes (efficacy and safety) between treatment group (oral salbutamol) and placebo group in the treatment of mild-moderate acute bronchiolitis”
• A Cochrane review (19) updated in 2006 recommending “Given the lack of data clearly supporting the efficacy of these agents, bronchodilators cannot be recommended for routine use in the treatment of bronchiolitis. This review of trials found a short-term improvement in respiratory scores in some infants treated as outpatients with bronchodilators. No significant benefit of bronchodilator treatment was noted among infants hospitalized for bronchiolitis. Large placebo-controlled randomized controlled trials that utilize consistent and validated outcomes are needed to settle the question of the effect of bronchodilators on acute bronchiolitis.
• The data from the Cochrane Review on safety of oral salbutamol: “[w]here adverse effects were reported, these were noted to be significantly or exclusively found in the study groups receiving bronchodilator(s)” Effects noted were tachycardia, decreased oxygen saturation, flushing, hyperactivity, tachycardia and prolonged cough, and tremor.
Use of oral salbutamol instead of inhaled salbutamol (12) in a study conducted in an inner city US setting should be considered as “higher level of inappropriate use, but not necessarily indicate the use of oral $\beta_2$-agonists instead of inhaled products, because of any problems in the manner of use or acceptability. The second reviewer commented, though “policy and practice dimension” is less easily addressed, none of the available studies on this aspect provide an argument for continuing to make available the wrong dosage forms of $\beta_2$-agonists.

His comment on cost of these products was “The cost implications of discontinuing the oral dosage forms would have to be considered by country programmes, taking into account their own particular circumstances”. The expert comments included cost of these preparations.

1. Salbutamol MDI (100μg/dose) – median price US$ 0.0090/dose (range 0.0056/dose to 0.0119/dose)
2. Salbutamol 2mg/5ml syrup – median price US$0.0051/ml (range 0.0023/ml to 0.0085/ml)
3. Salbutamol 2mg tablets/capsules – median price US$ 0.0023/tablet or capsule (range 0.0012/tab-cap to 0.0137/tab-cap)
4. Salbutamol 4mg tablets/capsules – median price US$ 0.0029/tab-cap (range 0.0018/tab-cap to 0.0085/tab-cap).

**Calculation: 100 microgram MDI: 2 mg in syrup: 2 mg in tablet = 3.9:2.2:1**

The subcommittee decided “Given the superiority of inhaled salbutamol over oral salbutamol for the management of asthma, the lack of evidence for the use of bronchodilators in bronchiolitis, and the paucity of evidence for the use of oral salbutamol in children with viral wheeze, the Subcommittee agreed that at present, oral Salbutamol should only be considered for use when treatment with inhaled asthma medications is not feasible. The EMLc was annotated to reflect this recommendation.

This current review is undertaken as an update of the 2008 review and expert comments given by the two reviewers on safety and efficacy of oral salbutamol preparations in the management of the wheezy child with acute respiratory tract infections and their role in the therapy of adults with asthma (See the components given in Introduction).
CURRENT PUBLISHED WHO GUIDELINES

Question: Current published WHO guidelines: What do they recommend for adults and children in the treatment of asthma? is it oral salbutamol or inhalational preparations?

Answer (Table 3, Annexure A):

Children:
Recommendation: Inhaled salbutamol dosage form
Alternative: If inhaled salbutamol is not available or not affordable, oral salbutamol (syrup or tablet)

Adults:

OTHER INTERNATIONAL GUIDELINES

Question: What do they recommend? Is it oral salbutamol or inhaled preparations? Is oral salbutamol recommended in treatment protocols?

Answer (Table 3, Annexure A):

Summary is given here. See Table 3 for further details

✓ None has recommended oral salbutamol straightaway
✓ All accept that oral salbutamol is inferior to inhaled salbutamol (Inhaled dosage forms: less side effect, quick action)
✓ Some has recommended oral salbutamol as an alternative when (1) inhaled dosage form is not available (20), (2), inhaled dosage forms are not affordable (20, 28), (3) patients are unable to use inhaled dosage forms (22), (4) asthma is mild and intermittent (23)
✓ Some has specifically stated that “oral salbutamol is not recommended” (21, 24)
✓ Some has mentioned only inhaled salbutamol with no comment on oral salbutamol (25, 26, 27)
✓ Some allows oral salbutamol as an alternative in adults than in children (22)
METHODS

Method adopted for Component 1 is given below.

Criteria for considering studies for the review

1. **Review question:** Safety and efficacy of oral salbutamol in the management of wheezy child with acute respiratory tract infections

2. **Definition of case:** wheezy child with acute respiratory tract infections = young children with viral related wheeze (presented by the Reviewer 2 in 2008 subcommittee meeting) = acute lower respiratory tract infection with wheezing = bronchiolitis

3. **Types of studies:** Randomized controlled trial

4. **Description of participants, intervention, control and outcome:**

   4.1. **Participants:** Studies which have recruited children under the age of 2 years with (wheezy child with acute respiratory tract infections = young children with viral related wheeze = acute lower respiratory tract infection with wheezing = bronchiolitis)

   4.2. **Intervention:** Oral salbutamol

   4.3. **Control:** Placebo

   4.4. **Outcome:** Symptom score, duration of symptoms, events of re-visit to hospital, events of hospitalization, frequency of adverse effects

5. **Exclusion criteria:**

   5.1. All studies which did not fit into above “PICO” were excluded (See Annexure B)

6. **Search methods for identification of studies**

   6.1. **Timing of search:** November 2010

   6.2. **Search database:** Pubmed

   6.3. **Search strategy:** Using a combination of MESH subject headings and text words relating to the use of salbutamol, Pediatric and randomized trial

   6.4. **Search term:** Update of what was done in 2008 (Reviewer 2): (salbutamol AND pediatr*) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]))
6.5. **Process of identification of studies:**

6.5.1. The titles of the results of above search term was reviewed and studies which fit into PICO and titles which do not give an idea about the PICO were selected.

6.5.2. Abstracts of the selected titles were reviewed and studies which fit into PICO or which do not give a clear idea about the PICO were selected.

6.5.3. Full Text articles of the selected abstracts were reviewed and studies which fit into PICO were selected for the review.

7. **Additional articles:** Two relevant Cochrane reviews were also reviewed.
RESULTS

Component 1: Safety and efficacy of oral salbutamol in the management of wheezy child with acute respiratory tract infections (See case definition in 6.2):

Summary of the results is given below. Details are available in Annexure B, Annexure C (Table 4) and Annexure D (Table 5).

Flow diagram for citations identified (See Annexure B)
- Five RCTs (16-18, 29, 30) and 2 Cochrane reviews (19, 31) were selected initially
- Three RCTs were identified for detail review (16-18)
- No new RCT was identified after 2008 search by the Reviewer 2
- Two RCTs (Both have been presented by the Reviewer 2 in 2008 Subcommittee meeting) were reviewed in detail (16,17)
- One RCT – Only abstract is available (Could not access the full text) – This study too has been presented by the Reviewer 2 in the 2008 Sub committee meeting (18)
- Both Cochrane reviews were summarized (one was presented by the Reviewer 2 in 2008 Subcommittee meeting) (19,31)
- Characteristics of 2 RCTs which were not subjected to detail review (29,30)
  1. Case definition: Acute cough (all non asthmatic coughs in children): Conclusion - In ambulatory children with acute cough who have no history of asthma and a normal chest examination, oral albuterol does not reduce the frequency or duration of cough (29)
  2. Intervention: Four groups (oral albuterol, oral placebo syrup, nebulized albuterol, saline nebulization): Conclusion: Albuterol is as effective as oral placebo in the management of bronchiolitis (33) – This study is included in one of the Cochrane review summarized in Annexure D (30)

Summary of efficacy and safety data of oral salbutamol in the management of wheezy child with acute respiratory tract infections (Annexure C, D for details)

- Two RCTs reviewed in detail (16, 17): Oral salbutamol (albuterol) was not superior to placebo in the treatment of bronchiolitis (mild to moderate). Adverse effects of tremor and vomiting were seen in the oral salbutamol group. Recommended discontinuation of practice of prescribing oral salbutamol for the symptomatic relief in the cases of mild to moderate bronchiolitis.
✓ One RCT (From abstract and 2008 Reviewer 2’s report) (18): *No differences in the beneficial or side effects* of salbutamol, or the number of days in hospital between the treatment groups and the control (Placebo) group.

✓ Cochrane review on “Bronchodilators for Bronchiolitis” (19): Bronchodilators produce small short-term improvements in clinical scores among infants with bronchiolitis and may slightly improve oxygenation in those treated as outpatients. However, given the high costs, incidence of adverse effects and uncertain efficacy based on the findings of this meta-analysis, *bronchodilators cannot be recommended for routine management of first-time wheezers who present with the clinical findings of bronchiolitis*. *Bronchodilators should not be used in patients who are hospitalized with bronchiolitis.* This review was not limited to oral salbutamol, but included bronchodilators in both (oral and inhaled) dosage forms – See Annexure C for details.

✓ Cochrane review on “Beta2-agonists for acute bronchitis” (31): *There is no evidence that beta2-agonists are useful in healthy children who have an acute cough, particularly if their lung examination is normal.* These children are more likely to have adverse effects than to derive any clinical benefit. Overall, there does not seem to be a clear benefit to adults either, although there is a trend toward some improvement in cough, especially in patients who have evidence of airway obstruction. This review was not limited to oral salbutamol, but included beta 2 agonists in both dosage forms – See Annexure D for details.

✓ SIGN: Inhaled beta 2 agonist bronchodilators are not recommended for the treatment of acute bronchiolitis in infants. (32)

**Component 2:** Oral salbutamol in the treatment protocols of Bronchial Asthma

Refer Page 11 and Annexure A for the results

**Component 3:** Information about price and availability of salbutamol preparations in resource poor settings

This section summarises some data (published and unpublished) on price and availability of salbutamol preparations in resource poor settings. As expected availability of inhaled dosage forms of salbutamol was poor in many resource poor settings. The major limitation is that most of these studies have not investigated the availability of oral salbutamol in the same settings. Hence there is no evidence of comparative data (availability of inhaled dosage forms vs. oral dosage form).
Cost data was also as expected – inhaled dosage form is more expensive than oral dosage form. Since it was less available in the public sector than the private sector, cost plays a crucial role as parents or patients have to buy the medicine from retail pharmacy.

An anecdote: Oral dosage form (syrup/tablet) can be bought for short duration (1 bottle of syrup approximately for 5 days (20 doses of 5 ml) or 15 tablets for 5 days), but inhaled dosage forms cannot be bought for short duration. It will be 200 doses in one unit – during a single episode of illness, parents/patients from resource poor settings would prefer to buy a cheaper 7 day treatment option (oral dosage form) than expensive 60 days treatment option (inhaled dosage form) as the money in their hand is limited. Similarly, in the public sector, where medicines are give free of charge, the Policy makers and Medical Administrators in resource poor settings would decide to procure and issue the cheaper 7 day treatment option (1 bottle/ 15 tablets can be given on discharge or in the OPD), rather than procuring and issuing expensive 60 days treatment option on discharge or in the OPD. Evidence of superiority of inhaled dosage forms is unfortunately weighed against its cost. A pharmacoeconomic analysis may even conclude that expensive 60 days option of inhaled dosage form would be more “cost effective” than the cheaper 7 days option of oral dosage forms. But these are not routinely done in resource poor settings.

1. **Capital city of 14 countries in Central Africa (32)**

“Salbutamol inhalers were widely available*, but spacer devices for their effective use in children were not**. Few participating countries reported that instructions for “home-made” spacer devices were routinely supplied. Beclometasone inhalers were rarely reported as available in public sector facilities and, when available in the private sector, they tended to be expensive. These observations raise questions about the management of respiratory illness. **Several national professional officers identified oral salbutamol preparations (i.e. syrup and tablets) as additional paediatric medicines that should be monitored in their countries.** These oral forms are used rarely in developed countries because of their limited effectiveness. Further work is needed to understand local treatment practices and preferences and to identify barriers to the more widespread use of metered-dose inhalers in children”

*: Central medical stores = 8/14  
**: Central medical stores = 1/14  
Salbutamol inhaler: 100 micrograms / dose (1 unit): Public sector 1.30–7.25 USD, Private sector: 2.07–7.47USD
2. Data from 5 States in India – Summary of findings and conclusion (33)

Public sector:
Availability: Salbutamol inhaler was available only in one state out of the five surveyed. Of the 20 public health facilities surveyed in that State, only 2 had the generic salbutamol inhaler. None had the innovator salbutamol inhaler
Procurement price: The median price for salbutamol was 0.56 times the IRP.
Affordability: This study does not measure the affordability of beclometasone and salbutamol in the public sector, as medicines are meant to be provided free of cost at public facilities. The surveys, however, indicate that availability is generally very poor at public facilities.

Private sector:
Availability: IB salbutamol inhalers were available in all the surveyed states, although the availability ranged from 20% to 95%. Availability of the generic version varied between 83% and 100%
Retail price: The median price of the IB salbutamol inhaler ranged from 0.86 to 1.12 times the IRP; the median price of the generic version ranged from 0.82 to 0.96 times the IRP.
Affordability: The daily wage of an unskilled government worker ranged from Indian rupees (INR) 130 to INR 150 (~US$3.50) in the states studied. Such a worker requires approximately 2 days’ wages to purchase a month’s treatment, i.e., one inhaler each of generic beclometasone and salbutamol. The majority of the Indian population, nearly 77% (~836 million), works in the unorganized sector, with an average salary of below US$0.50/day, approximately seven times lower than the daily salary of the lowest paid government worker. Essential inhalation medications for asthma are thus beyond the reach of the majority of the population.

Conclusion: Essential inhalation medicines for asthma were not available in the public sector where low-income populations receive treatment. Steroid inhalers were not readily available in the private sector. Essential inhalation medicines for asthma are not affordable for the majority of the population.

3. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis (34)

Salbutamol MDI 0.1 mg/dose – 200 doses/unit
a. Range of mean percent availability of any genetic product in the public sector in the survey countries (Table 3 in the article): 14-88.4%
b. Range of mean percent availability of any generic product in the private sector in the survey countries (Table 3 in the article): 47-79%
c. Median price ratios* of public sector procurement prices for lowest-priced generics (Table 4 in the article) – Overall: 0.89 (n=23) (0.43, 3.01)

d. Range of median price ratios* of originator brands and lowest-priced generics in the private sector, and of lowest-priced generics in the public sector in the survey countries (Table 5 in the article)
   i. Private sector – OB – 5.58-14.26
   ii. Private sector – LPG – 3.28-7.19
   iii. Public sector – LPG – 1.82-4.64

e. Range of mean number of day’s wages of the lowest-paid unskilled government worker needed to purchase a course of treatment by the WHO region of the survey countries (Table 6 in the article)
   i. Private sector – OB: 1.2 – 4.4
   ii. Private sector – LPG: 2.8 - 5
   iii. Public sector – LPG: 0.6-15


   a. Availability in public sector: Available in 3 out of 8 (37.5%) Teaching hospitals (Other level hospitals were excluded as inhalers are not supplied to those hospitals due to lack of Specialist Clinics)

   b. Availability in private sector: Available in 46 out of 48 private pharmacies (96%)

   c. Cost in private sector:
      i. MPR for OB: 2.264
      ii. MPR for LPG: 0.974
      iii. Affordability – Private sector: Data not available presently


<table>
<thead>
<tr>
<th>Medicine</th>
<th>Unit price</th>
<th>Cost of single dose</th>
<th>Cost for 5 days = 8 hourly for 5 days = 15 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salbutamol 2 mg tablet</td>
<td>0.07</td>
<td>0.07/ 2 mg</td>
<td>1.05</td>
</tr>
<tr>
<td>Salbutamol 4 mg tablet</td>
<td>0.09</td>
<td>0.09/4 mg</td>
<td>1.35</td>
</tr>
<tr>
<td>Salbutamol syrup 2 mg in 5 ml (100 ml bottle)</td>
<td>18.00</td>
<td>0.90/2 mg</td>
<td>13.50</td>
</tr>
<tr>
<td>Salbutamol aerosol Inhaler 100mcg/metered dose, 200 dose Unit</td>
<td>94.72</td>
<td>0.47/100 mcg</td>
<td>7.05</td>
</tr>
<tr>
<td>Breath induced device for dry powder capsules</td>
<td>30.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salbutamol dry powder Capsule for Breath induced device, 200mcg</td>
<td>1.7</td>
<td>1.7/200 mcg</td>
<td>25.5</td>
</tr>
</tbody>
</table>
Observations:
1. Single dose of salbutamol as syrup is more expensive than as aerosol. However, syrup can be purchased as 5 days treatment course (1 bottle), but aerosol cannot be bought for 5 days course. The whole unit (200 doses) of salbutamol aerosol is 5 times expensive than one bottle (20 doses) of salbutamol syrup.
2. Salbutamol tablet is very cheap – Most public hospitals tend to dispense tablets even to children in the OPD.
3. Dry powder capsules are relatively very expensive – For 5 days course, it is approximately 18 times more expensive than 4 mg oral tablet.

Conclusion (Component 3):
✓ Availability of inhaled salbutamol tends to be poor in resource poor settings, especially in public sector.
✓ Selling price in the private sector is beyond the reach of majority of population.
✓ (Children) In the public sector, the procurement price for a single dose – oral liquid dosage form (2 mg): aerosol inhaled dosage form (100 mcg): oral solid dosage form (2 mg) = 12.8: 6.7: 1
✓ (Adult) In the public sector, the procurement price for a single dose – Dry powder capsules (200 mcg) : aerosol inhaled dosage form (200 mcg): oral solid dosage form (4 mg) = 18.8: 10.4: 1
✓ However, inhaled dosage form has to be bought as an “entire unit” (200 doses), limits its wider availability in the public sector.

CONCLUSION

Component 1: Safety and efficacy of oral salbutamol in the management of wheezy child with acute respiratory tract infections

Efficacy: Oral salbutamol is not superior to placebo in providing symptomatic relief in infants with mild-moderate bronchiolitis.
Safety: Children on oral salbutamol are at risk of developing adverse effects such as tremor and vomiting.

Component 2: Oral salbutamol in the treatment protocols of Bronchial Asthma

Oral salbutamol plays a role in the therapy of asthma in children and adults. It is included in treatment protocols as an alternative to inhaled salbutamol when the latter is not available or not affordable.
**Component 3: Information about price and availability of salbutamol preparations in resource poor settings**

Availability of inhaled salbutamol is poor especially in the public sector where low income population receives treatment. In the public sector, availability of inhaled dosage forms is limited by high procurement prices of dry powder capsule and inability to procure aerosol inhaled dosage form as single dose/short course treatment. In the private sector, though availability of inhaled salbutamol is better than in the public sector, they are not affordable for the majority of the population.

**RECOMMENDATION**

Not to remove oral salbutamol (Tablet 2, 4mg, syrup 2 mg/5 ml) from the WHO Model EML

**Reason:** Oral salbutamol is required for the treatment of asthma in children and adults in resource limited settings as inhaled salbutamol tends to be unavailable or unaffordable in these settings.
References

7. BNF-C
13. Sri Ranganathan S, Fernandopulle R, Beneragama B V S H, Weerasinghe MC, Weeraratne ED. An Analysis of the pharmaceuticals issued by the Medical Supplies Division (MSD) over a period of five years; 2002-2006 - Sri Lanka: Joint publication of Department of Pharmacology, University of Colombo and Medical Supplies Division, Ministry of Health; 2009/2010
21. Global Strategy for the diagnosis and management of asthma in children five years or younger (2009) [www.ginasthma.org](http://www.ginasthma.org)
26. Best Treatment Guidelines for Bronchial Asthma (India) - *MJAFI, Vol. 63, No. 3, 2007*
27. Management of asthma – Guidelines by the Sri Lanka Medical Association; 2006
32. SIGN: Bronchiolitis in children - A national clinical guideline; November 2006. [http://www.sign.ac.uk](http://www.sign.ac.uk)
34. Kotwani A. Availability, price and affordability of asthma medicines in five Indian states. INT J TUBERC LUNG DIS 13(5):574–579
35. Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. www.thelancet.com Published online December 1, 2008 DOI:10.1016/S0140-6736(08)61762-6
### Annexure A:

**Table 3: WHO and other International guidelines for management of bronchial asthma: Recommendation on formulation of salbutamol**

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendation for oral salbutamol for bronchial asthma</th>
<th>Recommendation for inhaled salbutamol for bronchial asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Strategy for the diagnosis and management of asthma in children five years or younger (2009) <a href="http://www.ginasthma.org">www.ginasthma.org</a> (21)</td>
<td>Oral therapy is not recommended due to its slower onset of action and its tendency to produce more side effects</td>
<td>Rapid acting inhaled beta 2 agonists are the most effective bronchodilators available and therefore the preferred asthma reliever treatment for asthma in children 5 years and younger</td>
</tr>
<tr>
<td>GINA Report, Global Strategy for Asthma Management and Prevention (2009) <a href="http://www.ginasthma.org">www.ginasthma.org</a> (22)</td>
<td>Adult: Short acting oral beta 2 agonists are appropriate for use in the few patients who are unable to use inhaled medication. However, their use is associated with a higher prevalence of adverse effects <strong>Children:</strong> Oral therapy is rarely needed and reserved mainly for young children who cannot use inhaled therapy</td>
<td>Adult Rapid acting inhaled beta 2 agonists are the medications of choice for relief of bronchospasm <strong>Children:</strong> Rapid acting inhaled beta 2 agonists are the most effective bronchodilators available and therefore the preferred asthma reliever treatment for asthma in children 5 years and younger</td>
</tr>
<tr>
<td>British Guideline on the management of asthma Quick reference guide jointly by SIGN and the British</td>
<td>• Oral β2 agonists are not recommended for acute asthma in</td>
<td>Short-acting inhaled β2 agonists work more quickly and/or with fewer side effects</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendation for oral salbutamol for bronchial asthma</th>
<th>Recommendation for inhaled salbutamol for bronchial asthma</th>
</tr>
</thead>
</table>
| Thoracic Society (BTS)-2008 – Revised in 2009                            | • Oral β2 agonists have not been shown to affect symptom score or length of hospital stay for acute asthma in infancy when compared to placebo  
• β2 agonist tablets or syrup act as short acting bronchodilator in mild intermittent asthma | than the alternative |
<p>| <a href="http://www.sign.ac.uk">http://www.sign.ac.uk</a> (23)                      |                                                         |                                                          |
| American National Heart, Lung, and Blood Institute                        | Oral systemic beta2-agonists are not recommended        | Drugs of choice for acute bronchospasm. Inhaled route has faster onset, fewer adverse effects, and is more effective than systemic routes. |
| National Asthma Education and Prevention Program                          |                                                         |                                                          |
| Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma |                                                         |                                                          |
| Full Report 2007 (24)                                                    |                                                         |                                                          |
| electronic Therapeutic Guidelines (Australia).                            | Oral salbutamol is not mentioned                        | Only inhaled salbutamol is recommended                    |
| Pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources. World Health Organization, 2005 | Once the child has improved sufficiently to be discharged home, if there is no inhaled salbutamol available | Salbutamol by nebulizer or metered-dose inhaler. If salbutamol is not available, give subcutaneous epinephrine. Reassess |
| <a href="http://whqlibdoc.who.int/publications">http://whqlibdoc.who.int/publications</a> |                                                         |                                                          |</p>
<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendation for oral salbutamol for bronchial asthma</th>
<th>Recommendation for inhaled salbutamol for bronchial asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>(20)</td>
<td>or affordable, then oral salbutamol (in syrup or tablets) can be given</td>
<td>the child after 30 minutes to determine subsequent treatment: — If respiratory distress has resolved, and the child does not have fast breathing, advise the mother on home care with inhaled salbutamol or, when this is not available, oral salbutamol syrup</td>
</tr>
<tr>
<td>Best Treatment Guidelines For Bronchial Asthma (India) - MJAFI, Vol. 63, No. 3, 2007 (26)</td>
<td>Oral beta 2 agonists not mentioned</td>
<td>Patients with non-severe exacerbations can usually be managed on an outpatient basis, with repeated administration of rapid acting inhaled beta 2 agonists</td>
</tr>
<tr>
<td>Sri Lanka -1 (Sri Lanka Medical Association) 2006 (27)</td>
<td>Best through inhalers, may be given orally for mild cases- Side effects are more with tablets or syrups</td>
<td>Short acting beta 2 agonists - dosage form was not given (“Inhale route has faster onset and more effective”</td>
</tr>
<tr>
<td>Sri Lanka -2 (National best management guidelines – paediatrics (28)</td>
<td>Oral short acting β2 agonists are often used in Sri Lanka due to economic constraints.</td>
<td>The mainstay of therapy is short acting inhaled β2 adrenoceptor agonists</td>
</tr>
</tbody>
</table>

*Guidelines of IUATLD couldn’t be accessed*
Annexure B

Flow diagram for citations identified

(Salbutamol AND pediatr*) = 749

(Salbutamol AND pediatr*) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) = 261 titles

261 titles were searched - Selected titles indicating salbutamol/ albuterol + oral + non bronchial asthma indications + RCT and titles which didn’t give a clue to the PICO = 11 abstracts

11 abstracts were searched: Selected abstracts indicating oral salbutamol/ albuterol + placebo control + (bronchiolitis/wheezy child with acute respiratory tract infection/young child with viral related wheeze + acute lower respiratory tract infection with wheezing) + RCT and abstracts which have not clearly indicated the PICO = 5 full text articles (RCT)

Two reviewed in detail (16, 17), One – Only abstract was reviewed (18), Two excluded (19, 30)
### ANNEXURE C

**Table 4: Details of two RCTs reviewed in detail**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Country</strong></td>
<td>India</td>
<td>Canada</td>
</tr>
<tr>
<td><strong>Study setting</strong></td>
<td>Pediatric (OPD) of a tertiary care hospital</td>
<td>Emergency Department of a University affiliated paediatric hospital</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>double blind, randomized, placebo controlled trial,</td>
<td>double blind, randomized, placebo controlled parallel group trial</td>
</tr>
</tbody>
</table>
| **Study population** | • 140 infants with a clinical diagnosis of acute bronchiolitis  
• Included only mild cases  
• Viral studies was not done | • 129 infants with a clinical diagnosis of acute viral bronchiolitis  
• Included mild to moderate cases  
• 49 of the 61 tested were positive for respiratory syncytial virus (81% in test and 70% in control group) |
<p>| <strong>Intervention</strong> | Oral salbutamol (0.1 mg/kg/dose) (n=70) three times a day for 7 days or until complete resolution of symptoms, whichever was earlier | Oral albuterol (0.1 mg/kg/dose) (n=64) three times per day for 7 days or until complete resolution of symptoms, whichever was earlier |
| <strong>Control</strong>      | Placebo syrup (n=70)                                                                      | Placebo syrup (n=65)                                                                      |
| <strong>Follow up</strong>    | Children were followed up on day 3, 7, and 14 after enrolment.                             | Daily standardized telephone interviews were conducted until the infant had complete symptom resolution for a duration of 14 days whichever event was earlier |
| <strong>Primary outcome</strong> | Time to resolution of illness (ROI). This was defined as the time from study enrollment to the time the infant returned to baseline health status, as determined by principal caregiver. A 4-point scale was used for scoring the ROI. | Time to resolution of illness (ROI). This was defined as the time from study enrollment to the time the infant returned to baseline health status, as determined by principal caregiver. A 4-point scale was used for scoring the ROI. |
| <strong>Secondary outcomes</strong> | Duration of cough, cold, noisy breathing, time to resume normal feeding and time to resume normal sleeping, rates of revisit and hospital admission | Duration of cough, coryza, noisy breathing, time to resume normal feeding and time to resume normal sleeping, rates of revisit and hospital admission, ADR (tremor, vomiting) |
| <strong>Randomization</strong> | Satisfactory                                                                             | Satisfactory                                                                             |
| <strong>Blinding</strong>     | Satisfactory                                                                             | Satisfactory                                                                             |</p>
<table>
<thead>
<tr>
<th><strong>Loss to follow up</strong></th>
<th>Study group: Complete loss to</th>
<th>Study group: Withdrawals (W)= 2,</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>follow up (CLTF)=7</td>
<td>Major protocol deviation (MPD) = 8, Hospital admission (H) = 4</td>
</tr>
<tr>
<td></td>
<td>Placebo group: CLTF = 3</td>
<td>Placebo group: W =2, MPD=2, H=5</td>
</tr>
<tr>
<td>Results</td>
<td>1. Median ROI (SE, 95% CI) was 6 (0.5 to 7) days in the Salbutamol group as compared to 5 (1, 4 to 6) days in placebo group ($P=0.21$)</td>
<td>1. Median ROI (days) was similar: albuterol, 9.0 (8-13); placebo, 8 (7-9)</td>
</tr>
<tr>
<td></td>
<td>2. No significant difference in mean duration of fever, cough, coryza, noisy breathing, time to achieve normal feeding and normal sleep; and frequency of hospitalization or adverse effects</td>
<td>2. No significant group differences in any secondary outcome (time to normal feeding, normal sleeping, quiet breathing, resolved cough, and coryza)</td>
</tr>
<tr>
<td></td>
<td>3. ADR: tremors/trembling in 5 children (all from Salbutamol group), vomiting in 6 Salbutamol:2 placebo:4, irritability in 1 (placebo)</td>
<td>3. Health care revisit and admission rates were similar between group</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Oral salbutamol is not superior to placebo in providing symptomatic relief in infants with mild bronchiolitis.</td>
<td>No significant group differences either in primary or secondary outcomes in infants treated with albuterol versus placebo was found</td>
</tr>
<tr>
<td>Recommendation</td>
<td>Discontinuation of practice of prescribing oral salbutamol for the symptomatic relief in the cases of mild bronchiolitis.</td>
<td>The widespread use of albuterol in this patient group is not recommended</td>
</tr>
</tbody>
</table>

*Albuterol = Salbutamol*
Annexure D

Table 5: Summary of 2 related Cochrane Reviews

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Review title</td>
<td>Bronchodilators for bronchiolitis</td>
<td>Beta2-agonists for acute bronchitis</td>
</tr>
<tr>
<td>Review question</td>
<td>Are bronchodilators better than placebo in the management of bronchiolitis, as measured by improvement in clinical scores, oxygen saturation or admission to hospital?</td>
<td>To determine whether beta2-agonists are effective symptomatic treatment for patients without underlying pulmonary disease who present with acute bronchitis. (1) duration of symptoms, (2) distribution of adverse effects (3) Which sub groups will benefit from beta2-agonists</td>
</tr>
<tr>
<td>Justification for the review</td>
<td>(1) Widespread use of bronchodilators despite conflicting evidence regarding their efficacy (2) Three prior meta-analyses (Flores 1997; Hartling 2003; Kellner 1996) and a systematic review (King 2004) have shown that bronchodilators may improve clinical symptom scores but they do not affect disease resolution, need for hospitalization or length of stay</td>
<td>If beta2-agonists are effective for acute bronchitis then they should be more widely used. Surveys of US family physicians reported that only a small minority routinely prescribe beta2-agonists for this condition (Mainous 1996; Oeffinger 1998).</td>
</tr>
<tr>
<td>Type of studies</td>
<td>Randomized placebo-controlled trials of treatment with bronchodilators</td>
<td>Randomized controlled trials (RCTs) of participants diagnosed with acute bronchitis allocated to either a beta2-agonist or no beta2-agonists group</td>
</tr>
<tr>
<td>Type of participants</td>
<td>Infants and young children with bronchiolitis no older than 24 months.</td>
<td>Trials that enrolled patients who had a clinical diagnosis of acute bronchitis or acute cough unless the patients were: less than 24 months of age, known to have pre-existing pulmonary disease, known to have another acute respiratory illness</td>
</tr>
<tr>
<td>Types of intervention</td>
<td>Bronchodilator therapy: albuterol, ipratropium bromide and adrenergic agents. Routes of administration were: nebulized, oral and subcutaneous.</td>
<td>We included RCTs that assigned patients to a beta2-agonist (oral or inhaled) treatment or no beta2-agonist (no treatment, placebo or alternative treatment). The</td>
</tr>
<tr>
<td>Outcome</td>
<td>Clinical score, oxygen saturation, admission to hospital, duration of hospital stay.</td>
<td>Primary outcomes: Daily cough scores, the number of patients who were still coughing at the end of the trial and adverse effects</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Number of studies</td>
<td>22 = 17 trials were in infants wheezing for the first time, and 5 additional trials, in which results from participants with first-time wheezing could not be separated</td>
<td>Seven trials: Six RCTs compared beta2-agonists with placebo and one RCT compared a beta2-agonist (oral albuterol) with an antibiotic (erythromycin). The beta2-agonists were oral albuterol (or salbutamol), inhaled albuterol and inhaled fenoterol. Two trials had three groups: salbutamol plus dextromethorphan, dextromethorphan only and placebo</td>
</tr>
<tr>
<td>Number of participants</td>
<td>22 clinical trials studying 1428 infants with bronchiolitis</td>
<td>Children = 2 trials studying 134 participants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults = 5 trials studying 418 participants</td>
</tr>
<tr>
<td>Number of studies with oral salbutamol</td>
<td>2 trials had oral salbutamol with other forms of intervention</td>
<td>Children = 2 (N = 59, 75) (Albuterol syrup, Salbutamol syrup)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults = 3 (N=42, 142,108) Albuterol syrup, Albuterol tablet, Salbutamol</td>
</tr>
<tr>
<td>Number of participants in studies with oral salbutamol</td>
<td>Could not be separated</td>
<td>See above</td>
</tr>
<tr>
<td>Risk of bias in included studies</td>
<td>(1) 5 studies - inability to separate from the total population those included participants who were recurrent wheezers.</td>
<td>The quality scores, using the Jadad scale (Jadad 1996), were four in four trials, three in two trials and two in one trial</td>
</tr>
<tr>
<td></td>
<td>(2) Lack of standardized methods for outcome evaluation (timing of assessments, clinical scoring systems used) across the studies.</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>There was evidence of considerable heterogeneity for clinical score measures (dichotomized and average score) and oximetry, but</td>
<td></td>
</tr>
</tbody>
</table>

|--------------------------|----------------------|
| **Main results**
**“Bronchodilator versus placebo”**

1. In 8 trials, with 468 infants, there was no improvement in clinical score for 43% of those treated with bronchodilators compared to 57% of those treated with placebo (OR for no improvement 0.45, 95% CI 0.15 to 1.29).
2. There was a statistically significant but clinically modest improvement in the overall average clinical score (SMD - 0.48, 95% CI -0.62 to -0.33).
3. No statistically significant improvement in oxygenation overall (WMD -0.57, 95% CI -1.17 to 0.03)
4. Subgroup analyses showed a slightly greater effect size in outpatient studies, where there were shorter follow up durations, than in inpatient studies for both oximetry (outpatients WMD -0.84, 95% CI -1.59 to -0.10 versus inpatients WMD -0.25, 95% CI -1.18 to 0.67) and average clinical score (outpatients SMD -0.68, 95% CI -0.87 to -0.49 versus inpatients SMD -0.23, 95% CI -0.44 to -0.01)
5. Bronchodilator recipients showed no improvement in the rate of hospital admission after treatment as outpatients (18% versus 26%, OR 0.70, 95% CI 0.36 to 1.35) or duration of hospitalization for inpatients (WMD 0.02, 95% CI -0.32 to 0.36).

| **Trials in children: (2 trials)**
1. Neither trial involving children demonstrated any benefits from albuterol.
2. A non-significant trend towards shaking or tremor in children given albuterol versus those given placebo or only dextromethorphan (RR 6.76, 95%CI 0.86 to 53.18).
3. There were no differences regarding other adverse effects.

| **Trials in adults comparing beta2-agonists with placebo (4 trials)**
1. When the data from 3 trials were combined, there was no significant difference in presence of cough (control rate 71%; RR 0.86, 95% CI 0.63 to 1.18) or night cough (control rate 29%; RR 0.84, 95%CI 0.54 to 1.33) after seven days of therapy.
2. The combined data from 2 trials did not show a difference regarding the presence of a productive cough after seven days (control rate 52%; RR 0.76, 95% 0.32 to 1.84); combined data from 2 trials did not show a difference regarding whether patients were working or not after seven days (control rate 31%; RR 0.82, 95% CI 0.28 to 2.34).

| **Trial in adults comparing beta2-agonist with erythromycin (1 trial)**
patients given albuterol were less likely to have a cough or a productive cough after seven days than those given erythromycin; but...
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<tbody>
<tr>
<td></td>
<td>there were no differences in presence of night cough after seven days or in mean days until improvement in cough, well-being, or return to work or normal activities</td>
<td>The number of studies and total number of patients included (especially children) are small. Therefore, the review has limited power to detect differences between patients who were given beta2-agonists and those who were not. In the combined data of trials in adults, there was a trend towards improvements regarding cough, productive cough and night cough as well as in daily cough severity scores in patients randomized to the beta2-agonists. While these differences did not reach statistical significance, the confidence intervals were quite broad and include the possibility of clinically significant beneficial effects. For example, the possibility of up to a 46% reduction in cough after seven days for adults cannot be excluded given the low power of the combined results. The studies were also all of a short duration (three to seven days). Therefore, there is no information as to whether treatment with beta2-agonists would alter outcomes beyond this time. This is an important omission because many patients in these studies were still bothered by symptoms at the end of the trial.</td>
</tr>
</tbody>
</table>

**Conclusion**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Bronchodilators produce small short-term improvements in clinical scores among infants with bronchiolitis and may slightly improve oxygenation in those</td>
<td>There is no evidence that beta2-agonists are useful in healthy children who have an acute cough, particularly if their lung examination is normal. These</td>
</tr>
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</tbody>
</table>
| | treated as outpatients. However, given the high costs, incidence of adverse effects and uncertain efficacy based on the findings of this meta-analysis, bronchodilators cannot be recommended for routine management of first-time wheezers who present with the clinical findings of bronchiolitis. Bronchodilators should not be used in patients who are hospitalized with bronchiolitis. | children are more likely to have adverse effects than to derive any clinical benefit. Overall, there does not seem to be a clear benefit to adults either, although there is a trend toward some improvement in cough, especially in patients who have evidence of airway obstruction. This benefit, though, is not well-supported by the available evidence and must be weighed against the adverse effects of these medications, such as shaking, tremor and nervousness.
Conclusions for both children and adults are based on a relatively small number of trials and the confidence intervals in our analyses could not completely rule out the possibility of clinically significant beneficial effects of beta2-agonists. |
| Message for oral salbutamol | Since bronchodilators, overall, have shown to be of uncertain efficacy, oral salbutamol is not going to be different. In addition it will have more adverse effects than nebulized dosage forms | Majority of trials were with oral salbutamol (albuterol), hence the conclusions are for oral dosage forms as well |