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COUGH AND COLD REMEDIES FOR THE TREATMENT OF ACUTE RESPIRATORY INFECTIONS IN YOUNG CHILDREN

CHILD AND ADOLESCENT HEALTH AND DEVELOPMENT

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1. Introduction

Mothers often bring children with an acute upper respiratory infection to a clinic because of concerns about the child's cough, fever, sore throat, or blocked nose, or because of problems with feeding. Cough is a symptom of most acute respiratory infections (ARI) including both upper respiratory infections (URI), such as coughs and colds (also known as the common cold, coryza, acute nasopharyngitis or acute pharyngorhinitis), and the more serious lower respiratory infections (LRI) such as pneumonia, bronchitis and bronchiolitis. Medicines for the symptoms of upper respiratory infections are sought both for the relief of discomfort and as a response to the fear that the illness is potentially serious. Parents usually do not understand the mechanisms of these infections, and do not appreciate that a "cure" does not exist. The case management of ARI focuses on case detection and treatment of pneumonia but must also assure the adequate management of children with a cough or cold who do not have pneumonia (1–3). Health care providers spend a significant amount of time caring for children who present with these symptoms, and are under great pressure to treat them with "something". Their jobs are further complicated by the large number of preparations for cough and cold that are available, either by prescription or as over-the-counter preparations.

Respiratory tract infections are among the most important human health problems because of their high incidence and consequent economic costs. The number of ARI episodes (6 to 8) per child per year is similar in both developed and developing countries (4,5). The majority of respiratory infections are confined to the upper respiratory tract and most of these are simple coughs or colds. The mean duration of a simple upper respiratory infection in young children is 7–9 days (6). According to reviews of the medical literature (7), drug therapy for viral common colds produces few measurable benefits in adults. Symptomatic therapies, particularly oral or intranasal sympathomimetics, may provide short-term clinical relief, but all the available symptomatic treatments for common colds have associated side-effects. Nevertheless, persons afflicted with the common cold ingest a wide variety of over-the-counter preparations and prescription drugs, which they hope will cure the illness or relieve its symptoms, and many adults consider these remedies to be effective. Much of the therapy given to children is based on experience with these preparations in adults.

While it is clear that we are unable to cure the common cold, it is unclear how much we can really relieve the symptoms without risking toxicity in children. There is a growing consensus in the medical literature that many classes of preparations provide little (if any) relief of symptoms, and they exhibit significant undesirable effects. The latter are especially true in young children (less than 5 years

old). Cough and cold remedies are responsible for a significant proportion of emergency calls to poison control centres in the USA, and accidental ingestion by children as well as inadvertent overdosing by parents are often serious enough to warrant admission (8). Moreover, there are no data to suggest that these preparations prevent more serious disease (9). Of particular concern is the availability of cough syrups for children which contain alcohol. A survey of the labels and inserts of 142 cough syrups stocked in nine commercial pharmacies in Davangere, a town in south India, found that 23 of them contained from 2.8% to 20% of alcohol (10). Because of toxicity and drug interactions, alcohol should not be used in children's medicines. The World Health Assembly in 1987, noting that alcohol is present in many medicines, including medicines administered to children, urged Member States to review the registration of medicines containing alcohol as an active ingredient with a view to reducing its use as much as feasible (1).

Nevertheless, substantial sums are spent on cough and cold medicines in the developing world as well as in industrialized countries. It has been estimated that global sales in 1985 of over-the-counter medicines for cough and cold amounted to US$ 3000 million (excluding eastern European markets). In 1987, sales of cough and cold syrups in the Philippines totalled US$ 47 million; in the USA the total was more than $2000 million (11).

An ideal cough or cold medicine should alleviate a child's ARI symptoms in the recommended dosage without producing serious side-effects. It should not mask signs of concomitant infection, or cause sedation that interferes with the intake of food and fluids. Cold medicines should also be affordable and easy to administer. Carers should feel that the remedy recommended is appropriate for the child's illness. Rapport with the physician should encourage the carer to return if the child gets worse, or when the next episode of respiratory infection occurs (particularly if there are signs suggesting pneumonia).

This document reviews the efficacy and safety of cough and cold medicines in young children (under 5 years of age) with an acute respiratory infection. A systematic literature review (see Section 4 below) was carried out to identify appropriate randomized controlled trials (RCTs). The results of the relatively few RCTs which have been carried out in children are especially important. Results from trials carried out on adults cannot be reliably extrapolated to include children owing to important differences in their anatomy and immune responses and in the etiology of the common cold. The pharmacokinetics and toxicity of drugs in children are often different from those in adults. Plasma drug concentrations may differ substantially because of immature liver and kidney functions and differences in gastrointestinal absorption, plasma binding, and relative volumes of fat and water. As a general rule, the differences are more pronounced in infants and young children and in malnourished children (12,13).

It is also important to consider only trials of treatment of coughs and colds and not to extrapolate the findings from other conditions presenting with similar symptoms; for example, antihistamines are effective for controlling symptoms in allergic rhinitis but not for rhinorrhoea in the common cold.

The use of antipyretics and oral analgesics is not discussed in this document; the subject was summarized in another technical review paper entitled "The manage-

ment of fever in a young child with an acute respiratory infection" (14). The effects of cough and cold medicines in children with asthma, cystic fibrosis, or allergic disorders, as well as in adults with chronic conditions, are also not covered in the present review. This document does not discuss antibiotic treatment, which has no role in the management of children with the common cold because antibiotics do not shorten the duration of the illness and do not prevent complications or the development of pneumonia.

2. Pathophysiology of the common cold

The common cold is a self-limiting condition and must be distinguished from respiratory infections, such as pneumonia, otitis media and streptococcal pharyngitis, for which effective therapy does exist. These more serious infections have specific signs and symptoms which are not present in the common cold and which require specific antibiotic treatment (1–3). Almost all episodes of the common cold in the developed world are attributed to viruses, including rhinoviruses, parainfluenza viruses, influenza viruses, adenoviruses, respiratory syncytial virus and coronaviruses (15–17). Infection with one of the serotypes of rhinovirus accounts for up to 50% of colds in adults, but it is probably a less frequent cause of colds in children (18). No etiological agent can be identified in approximately 30% of common cold episodes (19). The same pathogens have been identified as causing colds in developing countries although etiological studies have been limited (20). Pneumonia, bronchiolitis, measles and pertussis can begin with symptoms resembling the common cold.

Symptoms attributable to the common cold include cough, runny nose, blocked nose, sore throat, fever, malaise, headache and loss of appetite (7,15,17). The pathology of the nasal mucosa varies depending on the causative organism. Rhinovirus infections are characterized by oedema and hyperaemia with transudative rhinorrhoea (18,21), but without direct damage of the columnar epithelium which is found with influenza virus infection (22). Children who develop viral rhinitis begin with a clear nasal discharge which rapidly becomes mucopurulent. This mucopurulent nasal discharge is commonly seen in colds with little or no change in the bacterial flora (23). Therefore, antibiotics are not indicated, and their empirical use does not provide any clinical benefit (23,24). Several randomized controlled trials carried out in both developing and industrialized countries have shown that antibiotic treatment does not prevent complications, or shorten the duration of the illness, or prevent the development of pneumonia (3,9,25–31).

Although the precise immunological and biochemical steps that produce cold symptoms have yet to be defined, several generalizations are possible. Bradykinin and lysylbradykinin have been found in the mucus of patients with experimentally induced rhinovirus infection and may be a common pathway by which nasal congestion and rhinorrhoea are produced (26). It is not known whether the same pathophysiological mechanisms operate when other viruses cause infection. Histamine-release mechanisms underlying allergic rhinitis play no role in the pathogenesis of rhinovirus infection (32–34).

3. Treatment of the common cold

Curative or prophylactic treatment

No drug therapy has been shown to cure or shorten the duration of viral upper respiratory tract infections. Among experimental therapies, alpha-2-interferon has shown some efficacy in preventing experimentally induced rhinovirus infections and their spread within families (35–37), but remains experimental due to expense and toxicity (38). Antiviral agents are available to treat specific infections—for example, acyclovir for herpes simplex, gancyclovir for cytomegalovirus, ribavirin for respiratory syncytial virus, and amantadine if given early in the course of influenza. However, these medications have no value in the management of a simple cough or cold. Despite its popularity, ascorbic acid (vitamin C) has not been shown to prevent or shorten the duration of colds, or reduce their symptoms (15,39). The evidence in favour of the action of zinc in reducing the duration of common colds is not yet convincing (40). There is no evidence that antibiotic or other medical therapy for the cold prevents pneumonia (9,25–31). Antihistamines and sympathomimetics do not reduce the incidence of otitis media following a cold; controlled clinical trials have shown no benefit from antihistamine or decongestant drug therapy for the prevention or treatment of otitis media (41,42) or otitis media with effusion (43–45), or for the prevention of Eustachian tube dysfunction (46).

4. Systematic literature review

Scientific evidence for the efficacy and safety of cough and cold remedies in children under 5 years of age is scanty. The difficulties inherent in evaluations of cough and cold remedies have been described in recent reviews (7,47). When studies examine the effects of combination drugs it is impossible to attribute specific effects to single drugs. Moreover, studies measure symptoms using subjective criteria that cannot be independently validated. The significance of the improvement reported in the studies is often difficult to interpret, particularly in studies involving a carer's assessment of a child's symptoms. Most studies reported in the literature have serious methodological flaws, including small sample size, inadequate control groups, lack of definition of the common cold, and failure to define outcome measurements.

In the light of these findings it is important to present the findings of a systematic review of the literature which assesses the quality of study design before commenting on the validity of the results. As the common cold is self-limiting, with symptoms resolving rapidly over a few days, it is essential that all treatment trials are placebo controlled. This review considers only randomized controlled trials meeting explicit quality criteria when assessing efficacy. However, it considers, in addition, descriptive studies reporting adverse effects.

4.1 Review of process methods

Randomized controlled trials (RCTs) were considered if they studied otherwise healthy adults and children with common cold symptoms, beginning within 48 hours of enrolment. The case definition of the common cold is symptoms of a runny and/or stuffy nose, sneezing, with or without symptoms of headache and cough. Studies of patients with allergic rhinitis, concurrent respiratory infection or other chronic disease, atopic eczema or asthma were excluded. Source populations were volunteers recruited from the community or at hospital or community outpatient clinics. Additional evidence was assessed from studies of healthy volunteers challenged with rhinovirus in experimental conditions.

Types of outcome measures varied among the studies but included both subjective and objective measures. Changes in the amount or duration of common cold symptoms—sneezing, nasal congestion, rhinorrhoea—were assessed subjectively with participants rating symptoms as absent, mild, moderate or severe, as well as giving a global evaluation of efficacy, such as complete relief, marked, moderate or slight relief, or no relief at all. Objective assessment included rhinometry to assess the mean nasal airflow, rhinoscopy to give a rating of the redness and swelling of the nasal mucosa, nasal secretions and nasal obstruction.

The search strategy sought to identify any trials, in the English language, of the treatment of the common cold. The Embase computer bibliographic database was used for trials from 1987 to 1999, and Medline from 1981 to 1999. The medical subject headings and keywords used are listed in Annex 1. These were supplemented by the Medline search from 1966 to 1991, reported by Smith & Feldman (48), and searches of the Cochrane database of Abstracts of Reviews and Effectiveness and the Cochrane Controlled Trials Register. Secondary references in identified papers and review articles were followed up. A presentation, workshop session and appeal for further articles at a major international conference on acute respiratory infections in Canberra, Australia, in 1997 was carried out in an attempt to identify unpublished trials. Finally, correspondence with recognized experts in the field requesting details of further published and unpublished data was undertaken. This last step included manuscript review by over 40 paediatricians known to have an interest/expertise in paediatric respiratory infections and by Cochrane Collaboration review groups who had completed or were in the process of carrying out systematic reviews of remedies for the common cold.

Each RCT was assessed according to predetermined criteria adapted from Smith & Feldman (48). These 11 criteria give a maximum score of 13 points and include study aim, subjects, randomization, blinding, dropout rate, measurements, and significance of outcomes (Annex 2). Only studies which scored over 70% were considered to be of sufficient quality to yield valid conclusions and are reported in this review.

4.2 Summary of overall findings

Only 34 RCTs meeting the above quality criteria were identified. Of these, only 5 were carried out in children. As there are so few trials of adequate quality in children, this review will report on findings of trials in adults also; however, the limited applicability of these data to children has already been noted (see Section 1). The few published RCTs in children, which meet the basic quality criteria of study design and reporting, form a totally inadequate database to support clinical practice. This is particularly regrettable considering the high volume of prescribed pharmaceutical agents for the common cold in children and the multimillion dollar investment by pharmaceutical companies on research in this field.

5. Relieving a cough

Acute episodes of cough are most often due to the common cold. Cough can be a symptom of upper or lower respiratory tract infection (49), or may be a consequence of a non-infectious condition such as asthma, exposure to cigarette smoke, or aspiration of a foreign body (50,51). The distinction between cough due to an upper respiratory infection and cough due to bronchitis is not important since both conditions in children are self-limited viral infections, and do not require antibiotic treatment (15). The distinction between wet and dry coughs or productive and non-productive coughs is of little therapeutic value, especially in children who usually swallow their sputum. Occasionally, the characteristics of a cough can give information about the likely cause of the illness—for example, prolonged coughing followed by a whoop is found in established pertussis infection and a barking cough is typical of croup.

Most children with a common cold or bronchitis cough. Coughing is a protective reflex, particularly when secretions are copious. Children with cough and fast breathing or chest indrawing may have pneumonia and should receive antibiotic treatment (1–3). Children with cough should therefore be assessed for any clinical signs that suggest pneumonia (fast breathing, chest indrawing) or danger signs of very severe disease (such as meningitis). In some children with asthma, cough (especially nocturnal cough) may be the predominant symptom and may be relieved by bronchodilator therapy.

Since non-productive cough is unusual in infants and young children, few of them require cough suppression. Parents and health workers should be discouraged from trying to eliminate this symptom. The cough reflex, which is a physiological response to airway irritation, functions to clear secretions from the respiratory tract and may therefore be beneficial. Retention of these secretions may lead to potentially harmful airway obstruction. Cough should therefore not be *eliminated* by drug therapy but can be *relieved* by a safe, soothing remedy. Practical observation suggests that a nocturnal cough associated with an upper respiratory infection is more commonly distressing to the parent than the child, and more frequently interferes with the sleep pattern of the adult. Rarely, a child may become exhausted or have insomnia or repeated vomiting due to cough. In these circumstances the use of a safe and effective cough suppressant would be helpful.

5.1 Centrally acting cough suppressants

Although there are many published RCTs of cough suppressants, the great majority of them are in adults with chronic bronchitis (30) and these are not considered in this review.

5.1.1 Codeine and other opiate derivatives (e.g. noscapine, hydrocodone, pholcodine)

Morphine is well recognized to be an antitussive but only at doses which cause marked sedation. Codeine, an opioid chemically related to morphine, acts on the cough centre of the medulla to depress the cough reflex, perhaps by increasing the cough threshold (30,52). Like other opioids, codeine has analgesic and sedative properties, but its action as an antitussive is achieved at lower doses than its analgesic and sedative effects (53).

Codeine, which has a half-life in the plasma of 2–4 hours, is metabolized by the liver and excreted in the urine, mostly in inactive forms. However, about 10% is demethylated to form morphine, which may be the active form of the drug (53,54). Young infants are more susceptible to codeine intoxication due to their immature hepatic glucuronidation system (43). Codeine is available in the sulfate and phosphate forms. It is sold alone in the form of syrup and capsules or tablets, or in combination with other medicines.

There are no published RCTs meeting the above quality criteria which evaluate these agents alone. One RCT (55) compared pholcodine (in combination with a decongestant) to codeine (plus a decongestant and an antihistamine) in 217 children. Both treatment regimens reported improved symptoms but no account was taken of any possible "placebo" effect. More side-effects were noted with the latter medication (which contained codeine).

Side-effects of codeine. Adverse reactions to codeine in nonintoxicated children include nausea and vomiting, constipation, palpitations and dizziness (43). After large doses, children may experience somnolence, rash, miosis (i.e. excessive constriction of the pupil of the eye), vomiting, itching, ataxia, and swelling of the skin. Respiratory failure leading to death has also been described (56). Some of these reactions can be attributed to a histamine-releasing effect which is dose-related (43,46). Prolonged ingestion of codeine can produce a state of narcotic dependency, and the drug may be subject to abuse (46).

Conclusion. Codeine preparations should not be recommended for the treatment of cough in young children.

5.1.2 Dextromethorphan

Although dextromethorphan is structurally related to morphine and codeine, it does not share their analgesic properties and has little sedative effect (44,46). Like codeine, dextromethorphan acts centrally on the cough centre in the medulla to elevate the threshold for coughing (44,46). The safe dose range seems to be considerably higher for dextromethorphan than for codeine (43).

Dextromethorphan is rapidly absorbed from the gastrointestinal tract. Its antitussive effect persists for up to 6 hours (44). Like codeine, it is metabolized in the liver and excreted in the urine, both unchanged and with demethylated metabolites (44).

Two RCTs in adults showed conflicting results. Tukainen et al. studied 108 adults and reported decreased nocturnal cough (57), while Thackray found that a combi-

nation treatment of dextromethorphan plus a decongestant and an antihistamine had no effect on cough among 70 adults (88). Three RCTs were reported in children and again show conflicting results. One trial evaluated dextromethorphan alone and found no effect (58), while two others with combination preparations including dextromethorphan (45,59) reported decreased cough and nasal symptoms. However, it is unclear which agent was responsible for these effects.

Side-effects of dextromethorphan. Untoward effects of dextromethorphan include dizziness and gastrointestinal disturbances (46). Like codeine, it can cause histamine release in sensitive individuals (43). In general, its toxicity is low. However, at high doses, dextromethorphan can cause central nervous system depression (44). Two reports of dextromethorphan intoxication in children (60,61) describe clinical findings of ataxia, nystagmus and disturbance in the level of consciousness. Neither case experienced respiratory depression, despite ingestion of nine and twelve times the recommended dosage.

Conclusion. Dextromethorphan appears to have little serious toxicity. Evidence of efficacy is conflicting. In studies in which cough suppression was reported, the effect was not marked. The only good quality RCT of dextromethorphan alone in children showed no effect (48). Given the conflicting nature of the evidence, no clear recommendation can be made in favour of its use. There may be a role for a therapeutic trial of dextromethorphan in the unusual circumstance in which severe prolonged coughing interferes with feeding or sleeping.

5.1.3 Antihistamines for cough

"Classical" antihistamines, now referred to as H1-receptor inhibitors, resemble histamine in structure and competitively inhibit the physiological effects of histamine stimulation at receptor sites (62–64). In addition to their use as anti-allergy drugs, H1-receptor antagonists often have anti-emetic, sedative and anticholinergic properties (53,54). Antihistamines are added to many cough and cold remedies as both antitussives and to treat rhinorrhoea and nasal congestion. A fuller discussion of the use of orally administered and topical antihistamines to treat nasal congestion is given in Sections 7.2.1 and 7.2.2.

Although some antihistamines may have an antitussive action, their clinical efficacy has not been well documented (43,65). Antihistamines do not appear to have any direct antitussive effect, but it has been proposed that they may act indirectly by reducing postnasal drip (41).

Side-effects of antihistamine drugs. Because histamine is similar in structure to biogenic amines such as acetylcholine, adrenaline and serotonin, it is not surprising that antihistamines may block the receptors of these other amines. For this reason, antihistamines exhibit anticholinergic activity and occasionally α-adrenoreceptor blocking activity. As there are few data about the pharmacokinetic properties of many widely-used antihistamines (52), and considerable variation in response among the population, particularly to its sedative effects (66), it may be difficult to determine the ideal dosage range.

Side-effects of antihistamines include central nervous system stimulation, extrapyramidal symptoms, antimuscarinic effects, and gastrointestinal disturbances (56).

The anticholinergic (atropine-like) action of antihistamines frequently causes a drying sensation in the throat and nasal passages and may result in thickening of bronchial secretions (43,56). Antihistamines also cause drowsiness, and diphenhydramine, the most sedating of the antihistamines, is used in non-prescription sleeping medications (54).

Antihistamines exhibit other actions apart from their abilities to inhibit the activity of histamine. They can both stimulate and depress the central nervous system. Central nervous system effects are the most common clinically important adverse effects of antihistamines (52). Paradoxical central nervous system stimulation has been found particularly in children, with irritability, insomnia, tremors, and occasionally convulsions (43). Paradoxical stimulation is occasionally seen with therapeutic doses, particularly in children, but occurs more often in drug overdose (52). Promethazine, a phenothiazine used as an antihistamine, may enhance sleep apnoea in infants and may contribute to sudden infant death syndrome (67).

Conclusion. Although antihistamines are thought to have antitussive effects and may be useful in some adult conditions, there is no clear evidence of cough suppression in children. Sedative effects and reports of paradoxical excitement in infants preclude their use as cough suppressants in children.

5.2 Soothing remedies (syrups) for cough

(See also section 8.1)

A demulcent is a liquid which coats the throat and soothes irritated mucous membranes. These preparations may help reduce coughing associated with a dry throat and are soothing to many patients.

Demulcents consist primarily of sugar. They may act by increasing saliva production and swallowing, thereby interfering with the cough reflex, or by coating the peripheral sensory receptors that trigger the cough (41). Soothing substances such as hot tea with honey and lemon, a syrup, or glycerol are harmless and inexpensive. The recipes for the simple linctus (cough mixture) of the British National Formulary and several other soothing cough preparations are listed in Annex 3.

There are no RCTs reporting the efficacy of demulcent syrups.

Side-effects of syrups. Some cough syrups contain as much as 40% alcohol, similar to the alcohol concentration of whisky. Alcohol may suppress the cough reflex by sedating the child. Some cough syrups also may contain a high level of sugar. If given in excess, they can cause an osmotic diarrhoea. Syrups should not be given to exclusively breastfed infants, as the sugar they contain may suppress an infant's appetite for breast milk.

Conclusion. Soothing (demulcent) syrups are cheap, popular and safe. Alcohol-containing syrups should never be used. However, simple, inexpensive syrups without alcohol may soothe the throat and can be recommended to provide some relief from cough in young children. They should not be administered to exclusively breastfed infants.

6. Clearing thick sputum

In theory, the two approaches for clearing thick sputum are by the use of:

- *Expectorants*, which aim to stimulate bronchial mucus production, thereby making the secretions easier to remove by cough or by ciliary transport (68).
- *Mucolytics*, which are designed to alter the viscosity of bronchial secretions, thereby making them easier to clear by cough or ciliary transport (56).

6.1 Expectorants

Expectorants are often prescribed to patients with a dry cough who complain that they cannot cough up mucus from their lungs. They may act indirectly by stimulating efferent vagal nerve fibres to bronchial glands, resulting in increased volume of bronchial secretions (69). Because vagal stimulation also irritates the gastric mucosa, large doses of expectorants such as guaifensin, ipecac, terpin hydrate, and ammonium chloride will cause nausea and vomiting. However, the notion that sub-emetic doses actually produce expectoration has been questioned (70). Expectorants such as guaifensin and potassium iodide act directly on bronchial glands to stimulate mucus production. Potassium iodide may also act as a mucolytic agent by breaking down mucoproteins and stimulating ciliary activity (59).

Expectorants are generally sold in combination with decongestants, antihistamines, bronchodilators and antitussives. Although expectorants are popular with patients and some physicians, many doctors remain sceptical of their efficacy, and these agents have shown little benefit in controlled studies (49,58,60). According to a recent critical review, expectorants—in order to be considered useful—should not only ease the removal of bronchial secretions, but also improve the patient's condition for the duration of treatment (71).

One published RCT of the expectorant guaifensin among 65 young adults met the stated quality criteria. It reported no change in cough or sputum thickness. There are no published RCTs of expectorants in children.

Side-effects of expectorants. The physiological response to an expectorant is affected by the person's general condition, state of hydration, condition of the respiratory tract, and by other drugs ingested with the expectorant (59). Large doses of expectorants irritate the gastric mucosa and may produce nausea and vomiting (58). Iodides can cause iodine reactions (skin eruptions, hypersensitivity reactions with angioedema, pulmonary oedema) in sensitive persons (72). Since iodides are taken up by the salivary and lacrimal glands as well as mucus cells, expectoration may be associated with rhinorrhoea, salivation and lacrimation (59).

Ammonium chloride is converted to urea in the liver, causing a metabolic acidosis and a mild diuresis (in larger doses it is used to treat metabolic alkalosis) (56). Terpin hydrate elixir preparations have a high alcohol content and therefore a potential for intoxication and abuse (59,62).

Some agents used as expectorants are potentially dangerous and should not be given to children. Chloroform was once widely used as an ingredient in cough syrups and other pharmaceutical products, but has been banned in over a dozen countries because of concerns about hepatotoxicity and carcinogenicity (73). Camphor is toxic and should not be ingested (see Section 10).

Conclusion. The addition of an expectorant with safe ingredients to a soothing syrup is of no proven benefit in children.

6.2 Mucolytic drugs

These include drugs containing a free thiol group, such as N-acetylcysteine, which work by breaking sulfhydryl bonds and directly thinning the sputum. Mucolytic agents are often administered by mouth or by inhalation to persons with chronic respiratory conditions characterized by excess mucus production, such as cystic fibrosis and chronic bronchitis (56). Although mucolytics alter sputum viscosity and may lead to subjective improvement in these patients, their use has not resulted in any consistent improvement in pulmonary function (30,56).

There are no published RCTs on mucolytic drugs meeting the stated quality criteria in either adults or children.

Side-effects of mucolytic drugs. Adverse effects reported following oral administration of acetylcysteine include bronchospasm, gastrointestinal disturbances and fever. Some antibiotics, including ampicillin, erythromycin, and some tetracyclines are physically incompatible with or may be inactivated by acetylcysteine (56).

Conclusion. While adjunctive therapy with a mucolytic may bring subjective improvement in persons with chronic respiratory diseases, there are no data to support their use in children with acute respiratory infections such as the common cold.

6.3 Oral hydration and mist therapy

Water and water vapour can promote expectoration of sputum, but opinions differ about its effect on the tissues of the respiratory tract. Some authors claim that water vapour acts as a mucolytic, and has a soothing action on the respiratory mucosa. Others, however, state that water is not readily incorporated into mucus when it is administered by inhalation, and that it may promote expectoration by an irritant action on the respiratory mucosa (74).

The value of steam and cold mist therapy as a mucolytic or expectorant has been questioned by some authors (64,75,76). A double-blind randomized study in which a group of adults and children breathed either steam (hot humidified air) or ambient air showed no beneficial effects on common cold symptoms. The group breathing steam demonstrated increased airway resistance and a fourfold increase in

side-effects, leading the authors to conclude that hot humidified air might actually damage the nasal mucosa of patients with the common cold (77). These findings were reinforced in a more recent RCT (78). Both of these trials utilized a nasal nozzle. There have been no RCTs evaluating humidifiers or vaporisers.

Side-effects of hydration and mist therapy. Cases of water intoxication after mist therapy with electronic nebulizers have been reported (66). Preparation of steam carries the risk of burns, both from fire and from failure to cool the steam. Finally, mist can induce bronchospasm in asthmatic patients (64,66,79).

Conclusion. Oral hydration is safe and beneficial. Increased fluids should be recommended for a child with a cough or cold. Given the lack of data supporting efficacy and the risk of injury associated with the production of steam, neither steam nor cold mist therapy should be encouraged in the management of a cough or cold.

7. Relief of nasal congestion and other cold symptoms

7.1 Sympathomimetic drugs

Most decongestants contain sympathomimetics in oral or topical form (drops and sprays) to reduce the swelling of the nasal mucosa and promote easier breathing. The decrease in blood flow and oedema presumably decreases nasal discharge as well.

7.1.1 Topical sympathomimetic drugs

Sympathomimetic agents imitate the actions produced by stimulation of postganglionic sympathetic or adrenergic nerves. These include stimulation of the heart and central nervous system, constriction of blood vessels supplying the skin and mucus membranes, and dilation of the bronchi (80,81). Sympathetic agents may act directly on adrenergic receptors, or indirectly by releasing stored norepinephrine from nerve endings. Some drugs such as ephedrine are both direct and indirect in their actions (69,70).

Topical sympathomimetic agents cause constriction of nasal blood vessels, thereby reducing mucosal swelling. Ephedrine, oxymetazoline, phenylephrine and phenylpropanolamine are used in local preparations for this purpose (70). Only two RCTs, both in adults, which met the quality criteria were identified. A study of oxymetazoline found reduced nasal symptoms (82), whereas a trial of tramazoline among 26 adults reported no difference from placebo. However, the small sample in the latter study means that the possibility of a false negative result cannot be excluded with any certainty. No RCTs of topical decongestants were identified in children.

Side-effects of topical sympathomimetic drugs. Topical agents when used for more than 2 or 3 days can cause rhinitis medicamentosa, a rebound congestion of the nasal mucosa (70,83). Nasal congestion may be as severe as, or worse than, the original symptoms, which is of particular concern in young infants who are obligate nose breathers. Therefore, topical decongestants should never be used in infants.

It is difficult to control the dose of topical agents, and young children risk toxicity from systemic absorption of nasal decongestants (84). Phenylephrine may cause local irritation when given topically (70). Therapeutic doses of oxymetazoline nose drops in infants and young children have reportedly caused central nervous system effects ranging from sedation to excitement and convulsive attacks resembling seizures (85).

Conclusion. Because of the difficulty in controlling dosage and the risk of serious side-effects, topical decongestants should not be used in the treatment of the common cold in infants and young children.

7.1.2 Orally administered sympathomimetic drugs

Oral sympathomimetics, including phenylephrine, pseudoephedrine, oxymetazoline and phenylpropanolamine, cause systemic vasoconstriction, reducing the volume of blood circulated to the nasal mucosa. Pseudoephedrine is a stereoisomer of ephedrine. It is similar to ephedrine in its action, but appears to have a less marked effect on blood pressure, and fewer central nervous system effects (69,70). Phenylephrine produces little central nervous stimulation, but increases the blood pressure, and is sometimes used as a pressor during anaesthesia (70). Phenylpropanolamine has an indirect action as a sympathomimetic. In addition to its use as a decongestant, it is an ingredient used in diet pills. It is structurally similar to amphetamine, a potent central nervous system stimulant.

Six RCTs in adults which met the quality criteria were identified. Three of these evaluated a decongestant alone against a placebo. Two studied pseudoephedrine (7,86), and one studied phenylpropanolamine. They were all found to be effective in relieving nasal symptoms. The other three RCTs studied ephedrine or pseudoephedrine in combination with other medications such as antihistamines and dextromethorphan (87–89). All three trials reported significant reduction in nasal symptoms.

Only two RCTs in children which met the quality criteria were identified. Both of these trials evaluated combination preparations containing the decongestant phenylpropanolamine (45,90). The results were conflicting, with one study reporting a significant decrease in nasal symptoms (45) and the other (among 96 children) reporting no difference compared with placebo (79).

Side-effects of orally administered sympathomimetic drugs. The adverse effects of sympathomimetics are essentially those of adrenergic stimulation (70). Psychic disturbances reported among children following phenylpropanolamine administration include irritability, sleep disturbances, hallucinations, aggressiveness (particularly in younger children), and seizures (91–95). Severe hypertensive episodes have been reported following phenylpropanolamine ingestion (70). Pseudoephedrine may have a higher margin of safety than other sympathomimetic agents. In a study of 81 965 prescriptions of pseudoephedrine to children under the age of 19, only one hospitalization (for a seizure) which could have been related to use of pseudoephedrine was identified (96).

Conclusion. Orally administered sympathomimetics may provide useful short-term relief of nasal congestion in some adults. As there are concerns about their efficacy and safety in young children, their use cannot be recommended. There are insufficient RCTs evaluating the efficacy of oral decongestants in children. The available studies report conflicting results and are difficult to interpret since combinations of medications were evaluated.

7.2 Antihistamine drugs

7.2.1 Orally administered antihistamine drugs

Antihistamines are the mainstay of therapy for allergic rhinitis (52,54), and the resemblance between cold symptoms and symptoms of allergic rhinitis led to the use of antihistamines for the common cold. However, since histamine is not present in increased concentrations in persons with upper respiratory infections, the rationale for their use in the common cold has been questioned (32,97,98).

Studies of the efficacy of antihistamines for treatment of cold symptoms in adults have had mixed results. West et al. reviewed 25 reports published between 1947 and 1975 and found 15 supporting antihistamine use for symptomatic treatment of the common cold and 10 that did not. They found serious problems in study design in most of the studies, and concluded that there was little valid evidence that antihistamines had any effect on the common cold (47).

The present review identified 12 RCTs in adults and 4 RCTs in children which met the quality criteria. The RCTs in adults comprised two studies from 1950 of thonzylamine, which were both negative (99,100); six trials of first-generation antihistamines—four of chlorpheniramine or dexbrompheniramine, all reporting significant symptom relief (47,101–103); one of doxylamine reporting symptom reduction (104), and one of triprolidine reporting no effect (86); and three of second-generation antihistamines—the two terfenadrine trials giving conflicting results (32,105) and the clemastine trial reporting significant symptom relief (106).

The four RCTs in children gave conflicting results. The only trial evaluating a second-generation antihistamine alone found no effect (107), while the three trials of antihistamines combined with decongestants showed relief of nasal symptoms with preparations containing triprolidine (86) and azatidine (49,90), but not brompheniramine.

An expert panel of clinicians and scientists concluded that while antihistamines were useful for allergy, "there are no convincing data to suggest antihistamines are of benefit in upper respiratory infection". The panel stated that their use either alone or in combination products to treat upper respiratory infections was "inappropriate", and that further study of their possible role in treatment of the common cold or otitis media was not warranted (108).

Side-effects of antihistamines (see Section 5.1.3). Promethazine, a phenothiazine antihistamine widely used for its anti-emetic and sedative properties, has been reported to cause agitation, hallucinations, seizures, dystonic reactions (109), sudden infant death syndrome, and apnoea (57). These adverse reactions are generally more severe and significant in infants (98), leading manufacturers to warn against administration in children under 2 years of age. However, the efficacy of promethazine as a sedative could lead to its misuse by parents who may have to cope with a screaming child. Second-generation antihistamines (see Table 1) have fewer anticholinergic side-effects and are considered not to sedate children in therapeutic dosages.

Conclusion. Oral antihistamines may provide a modest degree of symptomatic relief of sneezing and nasal discharge in adults with the common cold, although the results of trials are conflicting. However, their sedative effects and potential for

serious toxicity, and uncertain efficacy make them an unsuitable remedy for colds in young children. They are not effective in relieving nasal congestion or cough. Second-generation antihistamines have fewer anticholinergic side-effects, but do not have improved efficacy; indeed the evidence tends to suggest the opposite may be true.

7.2.2 Intranasal antihistamines

Gaffey and co-workers compared the intranasal administration of diphenhydramine and placebo in 23 adult volunteers as treatment for experimentally-induced rhinovirus colds (110). Nasal patency tended to improve after treatment with diphenhydramine, but the effect was of short duration and not statistically significant. The authors concluded that intranasally administered diphenhydramine in the dosage used (2 mg four times a day for 5 days) was ineffective compared with placebo in improving either the subjective or objective signs of experimental rhinovirus colds. However, the small sample size means that a clinically important effect cannot be excluded.

Conclusion. There are no data to establish the efficacy of intranasal antihistamines in young children. Their use should not be recommended.

7.3 Anticholinergic drugs

Anticholinergic agents decrease the production of saliva, as well as bronchial, nasal, gastric and intestinal secretions, and act as a bronchodilator. They include the tertiary ammonium compounds such as atropine sulfate and quaternary ammonium compounds such as ipratropium. There is considerable variation between individuals in susceptibility to atropine sulfate, severely limiting its therapeutic margin (111). Most remedies contain atropine in very low concentrations, for which efficacy has not been demonstrated.

Five RCTs in adults which met the quality criteria were identified. No trials were identified in children. Four trials evaluated ipratropium nasal spray alone (30,112), and one trial studied ipratropium nasal spray in combination with other agents. All trials showed significant symptom relief. The effect was most marked in the first 3 days and lasted 3–4 hours after administration. The reduced nasal discharge and sneezing did not, however, contribute greatly to the overall symptom score in many patients except when nasal discharge was prominent and troublesome.

Side-effects of orally administered anticholinergics. Side-effects include dryness in the mouth and gastrointestinal mucosa, mydriasis, cycloplegia (paralysis of the ciliary muscle of the eye), photophobia, tachycardia and cardiac arrhythmias, dizziness, urinary urgency and constipation. Children may be more susceptible to adverse effects. Atropine may provoke hyperpyrexia when the ambient temperature is high or when the child has fever.

Ipratropium nasal spray is reported to cause blood-tinged secretions in 10–15% of cases and nasal dryness, which can lead to irritation sufficient to result in stopping treatment in some adults.

Conclusion. The available evidence suggests that ipratropim nasal spray is effective in reducing nasal discharge and sneezing. Treatment can be recommended when excessive nasal discharge in adults is particularly troublesome. In other cases the modest effects in reducing sneezing and nasal discharge has to be balanced against the known adverse effects. Given their potential for significant side-effects and the lack of efficacy, cold remedies containing anticholinergics should not be used in young children.

7.4 Saline nose drops

No RCTs were identified which evaluated saline nasal drops. However, it has been reported that saline nose drops may be effective in softening dry or thick nasal mucus and clearing a blocked nose, although they do not appear to bring any overall improvement in the condition of children with colds (113). An easy way to administer them is by moistening a wick in clean, salted water and using it to drip a few drops onto the nasal mucus. Exact recipes, elaborate preparations and eye droppers are not needed.

Side-effects of saline nose drops. If too large a volume of drops is administered by dropper, infants may choke due to aspiration. There is one report of increased rates of bacteraemia in rabbits treated with saline nose drops (114). No data are available to suggest a comparable risk in humans .

Conclusion. Saline nose drops, administered by a moistened wick, are safe and may be an effective way to help clear a blocked nose.

7.5 Hot fluids

No RCTs were identified which evaluated oral hydration in reducing symptoms of the common cold in children. One study reported that in addition to having a soothing effect, hot fluids may increase the flow of nasal mucus (115). Another report suggested that hot beverages such as chicken soup may stimulate mucus production and loosen respiratory secretions, enhancing expectoration (59).

Conclusion. Although there are no data from RCTs to support the efficacy of hot fluids, their traditional use and soothing effect support the giving of warm teas or soups to children as soothing remedies.

8. Relief of sore throat

8.1 Soothing remedies (syrups and lozenges)

The reported soothing effect of a simple linctus (cough syrups) is believed to be due to the "coating" or lubrication of the posterior pharynx. Since inflammation of this area, as a result of either post-nasal drip or primary infection, is well documented, a soothing effect would appear to be logical and is commonly reported by people using these remedies. However no RCTs were identified, which have studied the efficacy of these preparations.

Side-effects of soothing remedies. See Section 5.2.

Conclusion. Inexpensive, soothing remedies such as a simple linctus or other cough syrup without harmful ingredients, or hot tea with honey and lemon can be used in young children, but should be avoided in young infants (or infants up to 4–6 months who are exclusively breastfeeding). Lozenges and hard candies should be avoided in young children due to the risk of aspiration.

8.2 Topical anaesthetic agents

Topical anaesthetics (benzocaine, dyclonine) are used to provide temporary relief of sore throat pain. They are available mainly as oral lozenges, but also as aerosols, gels or solutions. Many combine a topical anaesthetic agent with antiseptics (such as phenols, alcohol, cetylpyridinium or quaternary ammonium compounds) which are not effective in fighting viral or bacterial infections. No RCTs in young children meeting the quality criteria were identified.

Side-effects of topical anaesthetic agents. Lozenges should not be used in young children because of the risk of aspiration. Young children usually cannot gargle without ingesting the medicine. Overdoses of topical anaesthetics can cause nausea, as well as central nervous system and cardiovascular effects (116). There is concern that topical anaesthetic aerosols might occasionally precipitate bronchoconstriction.

Conclusion. Topical anaesthetic agents and lozenges may temporarily relieve sore throat symptoms in adults. However, because of lack of evidence of efficacy in pain relief and of concerns about potential toxicity, they should not be used in young children.

9. Use of combination drugs

Many commercial cough and cold remedies contain several ingredients, including cough suppressants, mucolytics, oral decongestants, antihistamines and expectorants. Most drug combinations in cough and cold remedies have no rational basis, e.g. ineffective ingredients or ingredients with opposing effects are often combined, such as an expectorant with a cough suppressant. Many contain a large number of ingredients, often in individually subtherapeutic doses or with similar therapeutic properties. Combination drugs such as these should be avoided. Cough syrups containing antibiotics, isoniazid (INH), bronchodilators or antipyretics should not be used.

Some combination drugs are justified for use by adults (or school-age children) if they combine effective and safe drugs intended to relieve two or more concurrent symptoms of the cold. For young children, however, such a combination cannot be justified. Combination products containing topical anaesthetic agents, mucolytic drugs, antihistamines, oral nasal decongestants, antitussives and anticholinergics should be avoided in young children. The American Academy of Pediatrics Committee on Drugs has advised against the use of combination cough and cold remedies (43).

10. Traditional cough and cold remedies

Most families prepare home remedies such as tea with honey or a mixture of one part lemon juice and one part honey. Several other ingredients are also common: tamarind, ginger and eucalyptus. Recipes vary widely. Traditional medicines derived from plants have been and will continue to be used for respiratory infections in many parts of the world (*117,118*). There have been few efficacy studies of traditional medicines as therapy for the common cold. A review of Chinese herbal medicines concluded that because of poor RCT methodology, it is difficult to recommend the use of these preparations in the management of the common cold. It proposed that well designed and conducted RCTs were required to assess these preparations further (*119,120*).

There is no reason to believe that a safe, soothing home-made remedy is less effective than a safe commercial remedy. Home remedies are usually inexpensive and promote self-reliance. Unlike commercial preparations, which may contain potentially harmful ingredients, most home remedies are harmless. Ingredients such as menthol and camphor may be used in topical preparations to be rubbed on the chest. However, these products may be toxic and should not be used in teas and oral preparations.

Conclusion. The use of safe, soothing home-made remedies for sore throat, such as lemon tea, should be encouraged.

11. Recommendations for management of a simple cough or cold or sore throat

The health worker should advise the mother about safe remedies which can soothe the child's throat or relieve cough or nasal congestion. National ARI, IMCI (Integrated Management of Childhood Illness) or child health programmes should decide whether to provide or prescribe a cough or cold medicine in the clinic, or advise the mother to prepare one at home. Policy options are summarized in Tables 2 and 3. Other aspects of essential home care advice, such as continued feeding, increasing oral fluid intake, and being alert for signs of pneumonia or other more serious illness, should be given due attention by the health worker when communicating with the child's parents or carers (121).

Health workers can safely recommend:

- Oral hydration (e.g. teas, hot soups).
- Relief of nasal congestion when it interferes with feeding; saline nose drops can be tried.
- Use of paracetamol for reduction of high fever when this distresses the child and for relief of pain.
- Safe, soothing remedies (e.g. simple linctus) are useful for both a cough and sore throat. Remedies can be commercially prepared, mixed at the health facility, or made at home.

These measures can be taken by the mother of any child with a cough or cold. Children with signs suggesting pneumonia should immediately be taken to a health worker for assessment.

It is important to educate mothers and health workers that a child's cough performs a useful function in clearing secretions from the airway and is not an illness in itself, which must be treated.

Although they have a role in symptomatic relief of recurrent allergic rhinitis, antihistamines are **not** indicated for relief of nasal congestion due to the common cold. Doctors often prescribe them for their sedative properties. However, cough or cold remedies containing atropine, codeine, alcohol or high doses of antihistamines may sedate the child sufficiently to interfere with feeding and the child's ability to clear secretions from the lungs.

Cough and cold remedies other than saline nose drops should **not** be given to young infants (less than 2 months old), or to exclusively breastfed infants (aged up to 4–6 months).

In addition to these statements about the use of cough and cold medicines for symptomatic relief of the symptoms of cough and cold, it should be noted that

there is no evidence that antibiotic or other medical therapy prevents pneumonia; antihistamines and sympathomimetics do not reduce the incidence of otitis media following a cold; and controlled clinical trials have shown no benefit from antihistamine or decongestant drug therapy in the prevention or treatment of otitis media (41,42) or otitis media with effusion (43–45), or in the prevention of Eustachian tube dysfunction (46).

12. Tables

Table 1 Drugs and remedies used for coughs and colds by pharmacological category

1. Antitussive agents

1.1 Centrally-acting cough suppressants

1.1.1 Opiate derivatives
- codeine
- hydrocodone
- noscapine
- pholcodine

1.1.2 Dextromethorphan

1.1.3 Non-narcotics
- carbentapentane
- chlophedianol hydrochloride

1.2 Aromatic topical antitussives (for external rub)
- camphor
- menthol
- eucalyptol/eucalyptus oil
- thymol
- turpentine

1.3 Steam inhalation antitussives
- camphor
- menthol
- eucalyptol/eucalyptus oil
- thymol
- turpentine

2. Clearing thick sputum

2.1 Expectorants
- ammonium chloride
- ammonium carbonate
- beechwood creosote
- benzoin preparations
- camphor
- chloroform
- guaifensin (glycerol guaiacolate)
- ipecacuanha (ipecac)
- potassium iodide
- sodium citrate

2.1 *Expectorants (continued)*
squill preparations
terpin hydrate
tolu balsam

2.2 **Mucolytic drugs**
acetylcysteine
bromhexine
carbocysteine

2.3 **Mist therapy**

3. Relief of nasal congestion and other cold symptoms

3.1 **Sympathomimetics**

3.1.1 Topical (nasal drops or spray)

- Phenylamines: desoxephedrine, ephedrine, phenylephrine
- Imidazole derivatives: naphazoline, oxymetazoline, xylometazoline

3.1.2 Oral
ephedrine (adrenaline)
phenylephrine
phenylpropanolamine (or nor-ephedrine)
pseudoephedrine

3.2 **Antihistamines**

3.2.1 First generation

- Alkylamines: brompheniramine maleate, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, pheniramine maleate, tripolidine hydrochloride
- Ethanolamines: diaphenhydramine, diphenylpyraline, doxylamine
- Ethylenediamines: methapyrilene, pyrilamine maleate, thonzylamine hydrochloride
- Phenothiazines: chlorpromazine, promethazine (fenergan), trimeprazine
- Piperazine: cyclizine, meclizine

3.2.2 Second generation
astemizole
terfenadrine
acrivastine

3.2.2 Second generation (*continued*)
loratidine
azelastine
acrivastine
clemastine

4. Anticholinergics:
atropine
belladonna
ipratropium
scopolamine

5. Saline nose drops

6. Hot fluids

7. Relief of sore throat

7.1 Demulcent or soothing remedies (syrups and lozenges), including traditional remedies
linctus
tea with honey and lemon
eucalyptus
ginger
tamarind
glycerin
menthol

7.2 Topical anaesthetic agents
benzocaine
dyclonine
lidocaine

7.3 Topical antiseptic agents
phenol compounds
hexybresorcinol

Table 2 Remedies that can be recommended or provided by the health worker

Policy options	Advantages	Disadvantages
1. Recommend a safe remedy which mothers can mix at home	Promotes self-reliance Inexpensive Discourages clinic visits for cold or cough alone Helps and soothes	Leaving the clinic empty-handed may discourage mothers from using the clinic again Mothers may mix a remedy that is not safe Remedy may not be valued Requires training of health workers to teach mothers, a task which they often do poorly
2. Give a safe remedy which is prepared or mixed at the health centre or is purchased commercially by the Ministry of Health	Mothers are pleased to get something from the health centre Safety is assured Inexpensive Helps and soothes	Preparation in the health centre requires ingredients, bottles and time Promotes dependency on the health centre

Table 3 Advice to be given by health workers on commercial remedies

Policy options	Advantages	Disadvantages
1. Discourage the use of potentially harmful remedies (antibiotics, combination cold remedies, vasoconstrictors, cough syrups with sedatives, medicated nose drops) Indicate which commercial remedies are not harmful and may be symptomatically helpful (e.g. a safe cough syrup)	May guide mothers to less harmful purchases Remedies are credible Remedies are available Mother feels she is doing something to help her child May help some symptoms Mothers will save money if they buy fewer and less expensive drugs	Mothers have to pay for remedies that are available commercially Promotes dependence on unnecessary drugs Health workers have to learn about different drugs
2. Discourage the use of all commercial remedies which mothers usually buy, including potentially harmful remedies and those with little benefit	Saves child from possible or probable harmful effects of drugs Saves money if families accept the advice	Drugs may appear to be helpful (e.g. clears nasal congestion, or sedates the child, or temporarily relieves cough or throat pain), and the mother may not trust the health worker's advice Takes up health worker's time Health workers must be taught what is in the drugs and what to say to discourage their use

13. Annexes

Annex 1 MEDLINE search strategy

(a) Search strategy to identify randomized controlled trials

randomized controlled trial.pt.
randomized controlled trials.sh.
controlled clinical trials.sh.
random allocation.sh.
double blind method.sh.
single blind method.sh.
(human not animal).sh.
clinical trial.pt.
exp clinical trials/
(clin$adj25 trial$).ti,ab.
(singl$ or doubl$ or trebl$) adj25 (blind$ or mask$)
placebos.sh.
placebo$.ti,ab.
random$.ti,ab.

(b) Subject headings and keywords to identify articles on the common cold

respiratory tract diseases
common cold
rhinitis
fever
rhinovirus

respiratory tract infections
pharyngitis
bronchitis
sputum
influenza

histamine H-1 antagonists
adrenergic alpha-agonists
expectorants
cholinergic antagonists
narcotics
drugs, non-prescription

sympathomimetics
propanolamines
antitussive agents
nasal decongestants
analgesics, non narcotic
anaesthetics, local

Annex 2 Quality criteria for assessing randomized controlled trials (RCTs)

research goals clearly defined
clear subject definition—age, diagnosis
randomized
intervention groups equivalent
clear definition of treatment
investigators blinded
subjects blinded
dropout rate low (<10%)
objective or well defined subjective measures
clear definition of statistical significance
consideration of alpha and beta errors

[For further details of scoring of quality criteria, see Smith & Feldman (48)]

Annex 3 Soothing remedies for cough or sore throat

- ***Simple linctus*** (British National Formulary)

Citric acid monohydrate 2.5%	1.25 ml
Concentrated anise water	0.5 ml
Amaranth solution	0.3 ml
Chloroform spirit	0.3 ml
Syrup	to 5 ml
Diluent syrup	

- ***Paediatric simple linctus*** is more dilute:

Simple linctus (as above)	1.25 ml
Syrup	to 5 ml
Diluent syrup	

- ***Soothing remedy***

Concentrated peppermint water	20 ml
Amaranth solution (1% aqueous)	5 ml
1% ammonium chloride	2 litres

- ***Glycerine, lemon & honey cough syrup***[a]

Ingredients

1. Honey, liquid type — 300 grams
2. Glycerin — 250 grams
3. Lemon juice to make final volume to 1 litre
4. (Optional) lemon pips boiled in the juice for bitter flavour
5. (Optional) food colouring, as desired. If a different colour would improve acceptance by patients, add some food colouring of the desired colour at the

[a] Recipe obtained from a product distributed by ECHO International Health Services, Coulsdon, Surrey, England.

end, i.e. after mixing all the other ingredients well. The flavour/colour can be altered by adding licorice liquid extract BP, 50 ml per litre.

Method

1. Squeeze the juice from the lemons, sufficient to produce about 400 ml of juice; strain through a cloth or strainer to remove any pips or lemon flesh.
2. Place the honey and glycerin together in a measuring jug.
3. Add the lemon juice to the honey and glycerin, sufficient to make final volume up to 1 litre.
4. Stir the ingredients together until well mixed.

■ ***Storage and shelf-life:***

Store away from light and heat (in a refrigerator if possible) in brown or opaque glass or plastic bottles, closed with airtight stoppers or caps.

Shelf-life, if made up exactly as in the recipe and stored cool: 2–4 weeks (but may be longer or shorter according to the local climate).

■ ***Lemon or lime drink***

Add the juice of three small limes (or one or two lemons) to a glass of drinking-water. Add one large spoonful of sugar to taste. Give one glassful three times daily.

■ ***Ginger drink***

Boil two matchbox-sized pieces of peeled root ginger (chopped or ground) in four glasses of drinking water for 15 minutes. Divide the solution into three parts and give one part every eight hours.

■ ***Tamarind drink***

Boil two tablespoons of finely chopped tamarind leaves in two glasses of water for 15 minutes. Strain and cool. Divide the solution into three parts and give one part every eight hours.

Annex 4 Calculating the quantity of camphor and other potentially toxic ingredients in cough and cold remedies

The constituents are usually presented as a percent which indicates the number of grams per 100 ml of remedy.

For example, one common mentholated balm contains 4.8% camphor or 4.8 grams per 100 ml = 4800 mg/100 ml.

One teaspoon (5 ml) therefore contains 240 mg. For a 10 kg child, a potentially lethal dose (50–500 mg/kg) would be 500–5000 mg or approximately 2–20 teaspoons.

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