Efficacy and Safety of Echinacea in Treating Upper Respiratory Tract Infections in Children

A Randomized Controlled Trial

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Context Echinacea is a widely used herbal remedy for treatment of upper respiratory tract infections (URIs). However, there are few data on the efficacy and safety of echinacea in treating URIs in children.

Objectives To determine if *Echinacea purpurea* is effective in reducing the duration and/or severity of URI symptoms in children and to assess its safety in this population.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled trial of healthy children 2 to 11 years old recruited from a regional practice-based network and an alternative medical center in 4-month periods from 2000 through 2002.

Interventions Study patients were randomized to receive either echinacea or placebo for up to 3 URIs over a 4-month period. Study medication was begun at the onset of symptoms and continued throughout the URI, for a maximum of 10 days.

Main Outcome Measures Primary outcomes were duration and severity of symptoms and adverse events recorded by parents; secondary outcomes included peak severity of symptoms, number of days of peak severity, number of days of fever, and a global assessment of severity of symptoms by parents of study children.

Results Data were analyzed on 707 URIs that occurred in 407 children, including 337 URIs treated with echinacea and 370 with placebo. There were 79 children who completed their study period without having a URI. The median duration of URIs was 9 days (95% confidence interval, 8-10 days); there was no difference in duration between URIs treated with echinacea or placebo ($P=.89$). There was also no difference in the overall estimate of severity of URI symptoms between the 2 treatment groups (median, 33 in both groups; $P=.69$). In addition, there were no statistically significant differences between the 2 groups for peak severity of symptoms ($P=.68$), number of days of peak symptoms (1.60 in the echinacea group and 1.64 in the placebo group; $P=.97$), number of days of fever (0.81 in the echinacea group vs 0.64 in the placebo group; $P=.09$), or parental global assessment of severity of the URI ($P=.67$). Overall, there was no difference in the rate of adverse events reported in the 2 treatment groups; however, rash occurred during 7.1% of the URIs treated with echinacea and 2.7% of those treated with placebo ($P=.008$).

Conclusions *Echinacea purpurea*, as dosed in this study, was not effective in treating URI symptoms in patients 2 to 11 years old, and its use was associated with an increased risk of rash.

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UPPER RESPIRATORY TRACT INfections (URIs) are a significant health burden in childhood. The average child has 6 to 8 colds each year, each lasting 7 to 9 days.[1-3] Symptoms frequently require medical attention; during the winter months almost 40% of visits to pediatricians by patients 1 to 5 years old are because of cold and cough symptoms.[4] Up to one third of young children with URIs are diagnosed with secondary bacterial infections such as otitis media or sinusitis, frequently resulting in antibiotic therapy.[2,4] To alleviate the symptoms of URIs, children are frequently given drugs such as decongestants, antihistamines, and cough suppressants.[5] Unfortunately, there is little evidence that these medications are efficacious in children younger than 12 years.[6-8]

Perhaps because of the lack of efficacy of conventional medications for URIs, a substantial proportion of children receive alternative forms of treatment such as homeopathy and naturopathy. It has been estimated that 11% to 21% of children in the United States and Canada who are receiving care from

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conventional clinicians are also using alternative therapies.[9-12] Much of this use is for treatment of respiratory and/or ear, nose, and throat symptoms.[9,10,12]

Echinacea, has been used extensively for the prevention and treatment of URIs.[13,14] It remains one of the most commonly used herbal remedies in the United States, with reported sales of more than $300 million annually.[15] Three species of echinacea are used for medicinal purposes: *Echinacea purpurea*, *E angustifolia*, and *E pallida*; *E purpurea* has been the most extensively used and studied species.[13] The beneficial effects of echinacea are thought to be due to its "immunomodulating" activity, most notably macrophage activation and enhanced neutrophil phagocytosis.[16,17] There have been a number of clinical trials of echinacea in treating or preventing URI symptoms in adults. In critical reviews and meta-analyses of these studies, most investigators have concluded that the evidence suggests echinacea may be an efficacious treatment for URIs,[18-20] but the conclusion is limited by methodological flaws in many of the studies.[18-20]

There are limited data on the efficacy and safety of echinacea in pediatric patients. Given the number of URIs in children and the lack of demonstrable benefit from conventional therapies, treatment with echinacea could potentially have a significant impact on young patients. Thus, we conducted a randomized controlled trial to determine the efficacy and safety of *E purpurea* in treating URIs in children 2 to 11 years old. Prior to the study, we postulated that treatment with echinacea would result in at least a 1.5- to 2-day reduction in the duration of URIs in children and that symptoms would be less severe than in patients receiving placebo.

METHODS

A randomized controlled trial was conducted by the Puget Sound Pediatric Research Network (PSPRN) and Bastyr University. The PSPRN is a regional practice-based research group in the Seattle, Wash, area. For this project, pediatricians from 7 private practices and 1 inner-city clinic participated. Bastyr University is an alternative medicine institution located in Kenmore, Wash.

Children 2 to 11 years old, without significant health problems, were eligible for participation in the study. Children with a history of asthma, allergic rhinitis, cystic fibrosis, and bronchopulmonary dysplasia were excluded as were patients with autoimmune disease because of the possible effects of echinacea on the immune system.[18] In addition, children with a history of an allergy to any related species and those receiving chronic medications of any kind or herbal, mineral, or specific vitamin supplements were excluded. Only 1 child per family was enrolled in the study.

Study patients were recruited for the project in 2 ways. At participating PSPRN practices, physicians discussed the study with parents of potentially eligible children at the time of an office visit. For those interested parents and children, the medical record was reviewed and exclusion criteria discussed to determine eligibility. A broader recruiting strategy was used at Bastyr University. Informational brochures about the study were distributed in the university's health care clinics and naturopaths' offices in the Seattle area; newspaper and radio advertisements were also used. After an initial screening, a history and physical examination were performed to ensure that the child was eligible.

At the time of enrollment, parents of study children completed a form that included demographic items such as the child's age, sex, and the number of other siblings in the family. Because of the possible effects on URI duration and severity, parents were also asked about the number of colds their child had experienced during the previous year, use of day care more than 20 hours per week, and presence of cigarette smokers in the household.

Each study child was enrolled in the project for a 4-month period between September and May 2000-2001 or 2001-2002; in Seattle, rhinoviral infections are most prevalent during this period of the year.[21] During the observation period, data were collected on up to 3 URIs in a study patient.

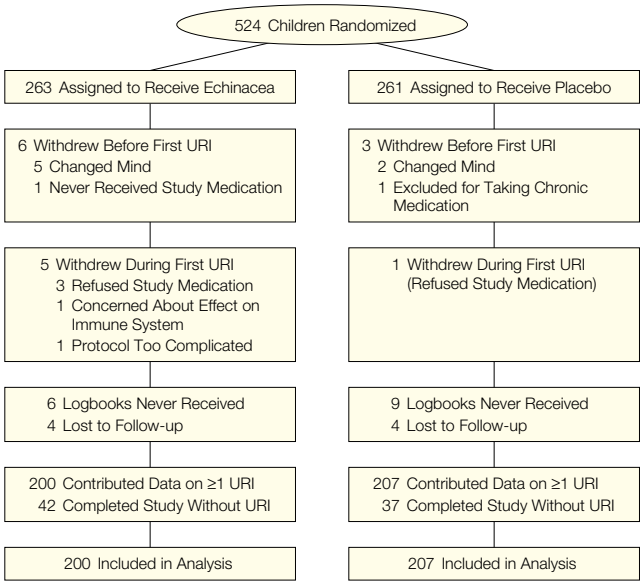
Each site was given a supply of study medication (echinacea and placebo) in consecutively numbered bottles that were identical in appearance. The contents of each bottle were randomly determined. Randomization was performed using a computer-generated randomization list and was stratified by site and in blocks of 10. As children were enrolled in the project, they were assigned a unique study number corresponding to the numbers on the bottles of study medication. The patient, parents, practitioner, and research staff were unaware of the contents of the individual bottles of study medication.

We used the dried pressed *E purpurea* juice of the above-ground herb harvested at flowering as the active study medication. This preparation was chosen because the extract has been used extensively in clinical and in vitro research.[22] We used an alcohol-free preparation; both an in vitro phagocytosis bioassay and chromatogram of the study medication indicated that it was equivalent to the fresh juice (data from Madaus AG, Cologne, Germany). The active medication was combined with syrup, while the placebo was syrup without active ingredients. The placebo was identical in appearance and similar in taste and smell to the active medication.

Dosing instructions were based on the recommendations of the manufacturer. Children 2 to 5 years old received 7.5 mL/d (3.75 mL twice a day) during a URI, while those 6 to 11 years old took 10 mL/d (5 mL twice a day). These doses provided 50% of the manufacturer's recommended adult dose in the younger group and 67% of the adult dose in the older group. The study medication was begun at the start of the URI and continued until all symptoms had resolved, up to a maximum of 10 days.

At enrollment, parents of study children received enough study medication for 3 URIs, symptom logbooks, and dosing spoons. Study coordinators telephoned parents shortly after enrollment and at 10- to 14-day intervals during the 4-month observation period to review study procedures and inquire about URI symptoms in the child. Par-

Figure. Flow of Children Enrolled in the Study



URI indicates upper respiratory tract infection.

ents were asked to call the study coordinator immediately when their child developed at least 2 symptoms of a URI, including sneezing, coughing, nasal congestion, runny nose, or temperature greater than 100.4° F (38.0° C). A study coordinator was available 24 hours a day, 7 days a week. Once the coordinator confirmed that the child met criteria for having a URI, the parent was asked to begin the study medication and to record information in the symptom logbook. The study coordinator contacted parents 1 to 3 additional times during the course of the URI to answer questions and inquire about any adverse events.

During a URI, parents were asked to monitor their child's symptoms daily during a standardized observation period from 5 PM to 8 AM. Each day, the parents recorded the severity of 4 symptoms (sneezing, coughing, nasal congestion, and runny nose) in the logbook using a 4-point Likert scale with possible responses ranging from "none" to "severe." To help standardize the ratings, a description of the different severities of each symptom was provided. Parents recorded the presence of fever in the child daily, based on either a documented temperature or a tactile assessment. The daily logbook assessment also included "other symptoms." A list of several possible symptoms was provided; parents were asked to write in any other symptom not included. Parents were asked to not give their child any medication other than the study medication and acetaminophen (if desired) unless prescribed by a physician. However, if another medication was administered, the parent was requested to record the name. Finally, parents recorded the times that they gave the study medication to their child. Parents completed the symptom logbook daily until they rated each of their child's symptoms as "none" for 2 consecutive days, up to a maximum of 21 days for each URI.

The primary study outcomes were duration and severity of URIs and adverse events. Duration was defined as the number of days between the start of the URI as recorded in the daily symptom logbook and the last day before all symptoms were recorded as "none" for 2 consecutive days. To assess severity, Likert scale responses for each of the 4 monitored symptoms were transformed to an ordinal scale, ranging from 0 for "none" to 3 for "severe." The daily severity score was determined by summing the scores for each symptom. The overall severity of each URI was computed by summing the daily scores for each day that symptoms were present. For days on which severity data were missing for a symptom, the severity score for that symptom was imputed by averaging the scores for the symptom from the preceding and following days.

The main assessment of the safety of echinacea was based on review of the daily symptom logbooks. Any indication in the logbook by the parent of any "other symptom" that the child experienced during a study URI was classified as an adverse event. To evaluate severity, parents were specifically queried about adverse events during each telephone call during the URI, using a standardized script to determine severity. An adverse event was considered "mild" if it did not interfere with routine activities, "moderate" if the symptom required the child to miss school or not participate in routine activities, and "severe" if the adverse event resulted in an urgent visit to an emergency department or necessitated hospitalization.

Secondary study outcomes included the peak severity of the URI (defined as the maximal daily severity score), number of days of peak severity, days of fever, and parental assessment of the overall severity of the URI in their child. A study patient was considered to have a day of fever when 1 or more temperatures of more than 100.4° F (38.0°C) was recorded in the logbook or the parent indicated that the child had a tactile fever. At the conclusion of a URI, the study coordinators contacted a parent of the study child and asked her or him to classify the severity of the URI as mild, moderate, or severe. At the end of the observation period, parents were asked to guess which treatment their child had received.

We used 2 measures to assess compliance with taking study medication. The main compliance measure was calculated as the number of doses recorded in the daily symptom logbooks divided by the number of doses that were indicated based on the duration of the URI. This assessment was validated by comparing the weight of bottles of study

medication for patients prior to and after their observation periods to determine the volume used. With both measures, a patient was considered to be compliant if he or she took at least 80% of the indicated doses.

The unit of analysis for statistical tests was the individual URI. Repeated measures techniques, including generalized estimating equation (GEE) regressions and repeated measure Cox marginal likelihood models, were used to account for multiple URIs in some study children. To compare the duration and severity of URIs treated with echinacea and placebo, Cox regression analysis for censored data was used. This regression technique was chosen because it accounts both for repeated URIs in the same child and missing data, such as occurred when parents failed to complete logbooks.[23] Linear GEE regression was used to assess differences between the 2 groups for the secondary outcomes of peak severity, number of days of peak severity, and number of days of fever. Due to skewed distributions of the data, a log transformation was performed on each of these variables. Logistic GEE regression was used to compare incidence of adverse events in the 2 treatment groups, and multinomial logistic GEE regression was performed to assess differences in parental global rating of severity of URIs treated with echinacea and placebo. For all of these evaluations, data were analyzed from all returned logbooks regardless of whether the patient was compliant with taking the study medication as prescribed. In addition, several subgroup analyses were conducted for the 2 primary outcomes.

Prestudy sample size estimations were based on simplifying assumptions. Some recruited patients would be expected to have no URIs during the study period, while others would have multiple URIs. However, we based sample size calculations on an assumption of 500 children each having 1 URI. With this sample size we would have a power of 80% to detect a 1.5- to 2-day difference in duration between URIs treated with echinacea and placebo (2-tailed α level = .05), assuming that the mean duration of URIs treated with placebos would be 7 to 10 days.

The study was approved by the institutional review boards of Children's Hospital and Regional Medical Center and Bastyr University. Signed written consent was obtained from parents of study patients; assent was obtained from children older than 7 years.

Table 1. Characteristics of Children Who Had at Least 1 Upper Respiratory Tract Infection (URI) During the Observation Period

Characteristic	Echinacea Group (n = 200)	Placebo Group (n = 207)
Age, mean (SD), y	5.6 (2.9)	5.4 (2.5)
Girls, No. (%)	102 (50.5)	100 (49.5)
No. of URIs in previous year, mean (SD)*	3.5 (1.6)	3.5 (1.5)
Children in day care, No. (%)†	29 (22.6)	18 (13.4)
Children in households with smokers, No. (%)	5 (2.5)	10 (4.8)
Children with siblings, No. (%)	156 (78.0)	159 (76.8)

*Data on previous URIs missing for 4 patients.
†Percentages based on children younger than 6 years at the time of enrollment: echinacea group, n = 128; placebo group, n = 134.

RESULTS

A total of 524 children were included in the study (FIGURE), including 311 enrolled by PSPRN pediatricians and 213 enrolled at Bastyr University. Overall, 92.7% of those children enrolled either contributed data on at least 1 URI or completed the study period without any URI symptoms. The Figure does not include 7 patients who dropped out of the study after contributing data on 1 URI. These included 1 child who moved out-of-state, 1 child whose parents were concerned about a possible citric acid allergy, and 1 child whose parents felt that the study protocol was too demanding. The parents of 1 patient, who received placebo, discontinued participation because they felt that the study medication was ineffective in treating their child's URI symptoms. Finally, 3 patients, all randomized to the echinacea group, dropped out of the study after contributing data from 1 URI because of the palatability of the medication.

A total of 759 confirmed URIs occurred in study patients; data were either not recorded in the logbooks or completed logbooks were not received for 52 URIs. Thus, logbook data were collected and analyzed on 707 URIs (93.9% of confirmed URIs) that occurred in 407 children. Children randomized to receive echinacea or placebo had similar characteristics (TABLE 1). There was a trend toward more use of day care in the echinacea group ($P = .09$); this analysis was limited to children younger than 6 years at the time of enrollment. Use of day care was not statistically associated with any change in the duration or severity of URI symptoms ($P = .50$ and $P = .79$, respectively). Overall, the mean (SD) age of patients with at least 1 URI was 5.5 (2.7) years; 49.6% were girls. The mean (SD) number of URIs in the previous year was 3.5 (1.5).

Among the 707 URIs for which data were collected, 370 were treated with placebo and 337 with echinacea. The difference in number of URIs treated with the 2 study medications is largely attributable to fewer second and third URIs among children randomized to the echinacea group. Of the children who had at least 1 URI, 64.4% of children in the placebo group had more than 1 URI compared with 52.3% of children receiving echinacea ($P = .015$ by χ^2 test).

There were no statistically significant differences between the 2 groups for duration of symptoms ($P = .89$), severity of symptoms ($P = .69$), peak severity of symptoms ($P = .68$), number of days of peak symptoms ($P = .97$), number of days of fever ($P = .09$), or parental global assessment of the severity of the cold ($P = .67$) (TABLE 2). Overall, parents continued to record data in the logbooks until all symptoms had resolved or through day 21 of symptoms for 608 URIs (86% of the total). After limiting the analysis to these 608 URIs, there was no statistically significant difference in duration of

symptoms among URIs treated with echinacea or placebo ($P=.90$). Among study patients 2 to 5 years old, the duration and severity of symptoms were similar in the 2 treatment groups ($P=.66$ and $P=.80$, respectively). The results were unchanged when use of day care was included in the regression models (difference in duration, $P=.69$; difference in severity, $P=.87$). There was also no difference between treatment groups for the duration or severity of URI symptoms in children 6 to 11 years of age ($P=.19$ and $P=.73$, respectively).

At least 1 concomitant medication, other than acetaminophen, was recorded as being administered to a study patient during 37.7% of URIs treated with echinacea and 34.3% of those treated with placebo ($P=.43$). The most common concomitant medications were over-the-counter cold remedies (decongestants, antihistamines, and/or cough suppressants) administered during 15.1% of study URIs; there was no significant difference in use of these products between the groups ($P=.56$). The use of oral antibiotics was also similar in the 2 treatment groups (8.9% of URIs treated with echinacea and 7.3% treated with placebo, $P=.48$). There was significantly more use of vitamin and/or mineral supplementation among children with URIs in the placebo group than in patients receiving echinacea (11.9% and 6.5%, respectively, $P=.04$). Conversely, antipyretics and analgesics other than acetaminophen were administered more commonly to children with colds treated with echinacea than placebo (9.8% and 5.1%, respectively, $P=.03$).

Table 2. Comparison of Treatment Outcomes in Upper Respiratory Tract Infections (URIs) Treated With Echinacea and Placebo

Outcome	Echinacea Group (n = 337 URIs)	Placebo Group (n = 370 URIs)	*P* Value
Duration of symptoms, median (95% CI), d	9 (8-10)	9 (8-10)	.89
Severity of symptoms, median (95% CI)*	33 (29-40)	33 (30-38)	.69
Days of fever, mean (SD)	0.81 (1.50)	0.64 (1.16)	.09
Peak severity of symptoms, mean (SD)†	6.0 (2.3)	6.1 (2.4)	.68
No. of days of peak severity, mean (SD)	1.60 (.98)	1.64 (1.14)	.97
Parental assessment of severity, No. (%)‡			
Mild	153 (46.5)	170 (46.3)	.67
Moderate	128 (38.9)	157 (42.8)	
Severe	48 (14.6)	40 (10.9)	

Abbreviation: CI, confidence interval.
*Severity calculated by sum of daily symptom scores (range, 0-12).
†Highest daily severity score recorded during a URI.
‡Percentages based on 367 responses to URIs treated with placebo and 329 treated with echinacea.

Table 3. Adverse Events Reported in Daily Logbooks by Parents of Children With Upper Respiratory Tract Infections (URIs) Treated With Echinacea or Placebo*

Adverse Event	No. (%) Echinacea Group (337 URIs)	No. (%) Placebo Group (370 URIs)	*P* Value†
Any adverse event	152 (45.1)	146 (39.5)	.14
Itchiness	13 (3.9)	7 (1.9)	.14
Rash	24 (7.1)	10 (2.7)	.008
"Hyper" behavior	30 (8.9)	23 (6.2)	.31
Diarrhea	38 (11.3)	34 (9.2)	.35
Vomiting	22 (6.5)	21 (5.7)	.56
Headache	33 (9.8)	24 (6.5)	.11
Stomachache	51 (15.1)	41 (11.1)	.16
Drowsiness	38 (11.3)	36 (9.7)	.52
Other	63 (18.7)	48 (13.0)	.06

*Values presented as number and percentage of URIs in each treatment group in which the adverse event was reported on at least 1 day in the daily logbooks.
†*P* values were calculated after adjusting for multiple URIs in the same child.

Study medication bottles were returned by parents of 278 children, who contributed data on 498 URIs. Among these patients, 238 (85.6%) had compliance reported in the logbooks of at least 80%; this compliance was verified by a determination based on changes in bottle weights before and after the observation period in 229 children (96%). Overall, reported compliance with administering study medication as prescribed was at least 80% for 620 (87.6%) of the 707 study URIs, including 85.8% of URIs treated with echinacea and 89.5% of those treated with placebo ($P=.16$). After limiting the analysis to the 620 URIs in which patients received at least 80% of the prescribed study medication, there was no difference in the duration ($P=.68$) or severity ($P=.41$) of symptoms between the groups.

At least 1 adverse event was reported during 42.5% of study URIs, with no significant difference between the 2 treatment groups ($P=.14$) (TABLE 3). Rash was reported during 7.1% of URIs treated with echinacea and 2.7% of those treated with placebo ($P=.008$). Parents were also asked about adverse events through telephone contacts during URIs in their children. There was at least 1 telephone contact with parents of study patients during 704 of the 707 URIs; the median interval from the first day of study medication until the first contact was 3 days (range, 2-17 days). One or more adverse event was noted through this mechanism during 22.8% of URIs, including 25.6% of those treated with echinacea and 20.8% of those in which placebo was administered ($P=.06$). In the echinacea group, 77.3% of adverse events were categorized as mild and 21.2% as moderate; the percentages were similar in URIs treated with placebo ($P=.89$). Two children had a serious adverse event, the sudden onset of stridor after receiving a dose of study medication that was severe enough to necessitate a visit to an emergency department; both of these patients were treated as outpatients with oral steroids. Both patients were receiving echinacea, and both were excluded from further participation in the study.

Parents of 398 of the 407 study patients who had at least 1 URI were contacted at the end of the observation period and asked to guess which medication their child had taken. Among those parents whose children were randomized to the echinacea group, 35.1% correctly guessed that their child had received the active medication, 22.7% thought that their child had taken placebo, and 42.3% indicated that they didn't know which medication they had received. The results were similar among parents of placebo recipients; 33.8% thought that their child had received echinacea, 25.5% placebo, and 40.7% did not know.

The sample of 707 URIs in 407 children provided an 80% chance to detect a 2-day difference in duration of symptoms in URIs treated with echinacea and placebo, given a median duration of 9 days in the placebo group (2-sided α level = .05).

COMMENT

The results of this study demonstrate that *E purpurea*, in the dosing regimen used, was not effective in shortening the duration or decreasing the severity of URIs in children 2 to 11 years old. Despite multiple subanalyses, we did not find any group of children in whom echinacea appeared to have a positive effect. We also found no differences between echinacea and placebo for secondary study outcomes. Echinacea was generally well tolerated. However, although rash was only reported during 7.1% of URIs in children treated with active medication, this was a significantly greater frequency than in placebo recipients; the *P* value for the difference was sufficiently low (.008), suggesting that this was actually an adverse effect of treatment with echinacea.

To our knowledge, this is one of the largest randomized controlled trials of echinacea in pediatric patients, and perhaps one of the largest conducted on patients of any age. In addition to our large sample size, the validity of the results is strengthened because of several aspects of the project. First, we enrolled patients who seek care from both traditional and alternative providers in an attempt to negate the effects of preconceived biases about echinacea. The "blinding" procedures worked well; virtually equal proportions of parents of children receiving echinacea and placebo guessed that their child received active medication, while the biggest proportion indicated that they "couldn't tell" which medication their child received. In addition, through extensive telephone contacts and the ability to talk with a study coordinator 24 hours each day, we collected data on a high percentage of URIs and were able to ensure that the medication was started early in the course of the illness. Finally, our results were the same whether we used standardized definitions for severity or a global assessment of severity by parents of study children.

Other placebo-controlled trials on the efficacy of echinacea in treating URIs have all been conducted in adults and have had mixed results. In 2 trials using products similar to that used in our study, patients receiving echinacea had significantly shorter and less severe URIs than placebo recipients.[24,25] Other investigators have used *E pallida* root,[26] mixtures of *E purpurea* root and herb,[27] and mixtures of *E purpurea* root, herb, and *E angustifolia* herb[28]; in each of these studies the active medication was found to be more effective than placebo in decreasing duration and/or severity of URIs. However, it is difficult to generalize the results of these trials because of significant methodological issues, including problems with randomization, the adequacy of blinding, and analytic techniques.[18-20] In a more recently published study, Barrett et al[29] found no difference between a mixture of *E purpurea* root and herb and *E angustifolia* root and placebo in relieving URI symptoms.

There are several possible explanations for our finding of a lack of efficacy of echinacea in treating URIs in children. It is thought that echinacea therapy should be initiated at the first signs of a URI to be effective.[30] Although we designed our trial so that the study medication could be begun in a timely manner, it is conceivable that if the medication were started even earlier in the course of the illness, we may have found benefit. In previous trials with positive results using products similar to that used in our study, treatment was begun when patients had a subjective feeling of a cold, rather than requiring a minimum of 2 symptoms.[24,25] Because the active ingredients in echinacea have not been standardized, it is difficult to determine the optimal dosing regimen in children. We may have had different results in our study if we had used a different species of echinacea or different preparation of *E purpurea*, if we had used a larger dose of medication, or had used a different dosing schedule.

Finally, one of the most vexing problems in conducting research on symptomatic relief in children is adequately assessing outcomes. Not only is the assessment secondhand (ie, made by the parent instead of the child), fewer symptoms can be evaluated than in trials of adults. In addition, although the scoring system we used for assessing symptoms was based on criteria developed and validated in adults,[31] there are, to our knowledge, no scoring systems that have been validated in children. These inherent problems may explain why similarly designed trials of zinc gluconate for the treatment of URIs had positive results when adults were studied,[32] but negative results in children.[3]

Our study had an 80% power of detecting a decrease of approximately 20% in duration of URI symptoms in those patients receiving echinacea. This is a smaller effect size than that observed in previous trials.[24-26,28] It is possible that echinacea, as used in our study, may have had a small benefit in reducing the duration of symptoms that might have been detected with a larger sample size.

Although we attempted to exclude children with known allergies to echinacea species or those with other atopic conditions from participation, it is possible that the increased rate of rash seen in children whose URIs were treated with echinacea was a manifestation of an allergic reaction. Severe allergic reactions to echinacea, including anaphylaxis, have been reported.[33] It is possible that the 2 children in our study

who developed croup symptoms shortly after taking a dose of echinacea may have been experiencing an allergic reaction. However, this result could also have easily been a chance occurrence; croup is not an uncommon disease in young children with URI symptoms.[34] Further, placebo-controlled studies in adults have not documented any increase in rash or allergic reactions among echinacea recipients.[20,24,25,27,29]

The statistically significant reduction in the number of subsequent URIs in children receiving echinacea compared with placebo recipients may be a spurious finding, given the multitude of outcomes examined. We had not planned on conducting this analysis prior to the study. However, the result is intriguing. It is conceivable that echinacea stimulated an immune response in study children that was too late to modify the URI for which it was given but provided a window of protection against another URI in the child. In one study, an echinacea preparation similar to that used in our trial was effective in preventing URIs in patients 13 to 84 years old, when given over an 8-week course.[35]

Given its lack of documented efficacy and an increased risk for the development of rash, our results do not support the use of echinacea for treatment of URIs in children 2 to 11 years old. Further studies using different echinacea formulations, doses, and dosing frequencies are needed to delineate any possible role for this herb in treating colds in young patients. Our finding that echinacea may be effective in preventing URIs also deserves additional study.

Author Contributions: As principal investigator, Dr Taylor had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Taylor, Standish, Calabrese.
Acquisition of data: Weber, Standish, Quinn, Goesling.
Analysis and interpretation of data: Taylor, Weber, Standish, McGann, Calabrese.
Drafting of the manuscript: Taylor.
Critical revision of the manuscript for important intellectual content: Taylor, Weber, Standish, Quinn, Goesling, McGann, Calabrese.
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