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# Safety and Tolerability of North American Ginseng Extract in the Treatment of Pediatric Upper Respiratory Tract Infection: A Phase II Randomized, Controlled Trial of 2 Dosing Schedules

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The authors have indicated they have no financial relationships relevant to this article to disclose.

## What's Known on This Subject

COLD-fx is the number 1 natural health product sold in Canada and was introduced recently to the US market. Adult safety and efficacy data have been published; however, the dose, tolerability, and safety of this product in children are unknown.

## What This Study Adds

A randomized, double-blind dose-finding 3-arm trial demonstrated that standard doses of the study product were well tolerated and merit additional evaluation with regard to treatment of pediatric URTI.

## ABSTRACT

**BACKGROUND.** Upper respiratory tract infections are the most common childhood illness. *Panax quinquefolius* (American ginseng root extract) standardized to contain 80% poly-furanosyl-pyranosyl-saccharides is purported to be effective in adult upper respiratory tract infection but has not been evaluated yet in a pediatric population.

**OBJECTIVES.** Our primary objective was to document the safety and tolerability of 2 weight-based dosing schedules (standard dose versus low dose versus placebo) in children. We also used the Canadian Acute Respiratory Infection Flu Scale, a quantitative scoring sheet for measuring the severity and duration of upper respiratory symptoms, to establish the SD of the treatment effect to allow sample-size calculations for future clinical trials.

**METHODS.** We conducted a randomized, double-blind dose-finding 3-arm trial (2 dosing schedules of American ginseng extract with 1 placebo control) during the winter months (November 2005 to March 2006) in children 3 to 12 years of age.

**RESULTS.** Seventy-five subjects were prerecruited from the general population in Edmonton. Of these, 46 subjects developed an upper respiratory tract infection and were randomly assigned (15 standard dose, 16 low dose, and 15 placebo), with 1 subject withdrawing from the low-dose arm before beginning the intervention. No serious adverse events were reported. The frequency, severity, and degree of association between the intervention and reported adverse events were not significantly different among each of the 3 treatment arms.

**CONCLUSIONS.** Standard doses of ginseng were well tolerated and merit additional evaluation with regard to treatment of pediatric upper respiratory tract infection. *Pediatrics* 2008;122:e402–e410

**U**PPER RESPIRATORY TRACT infections (URTIs) have been documented as the most common reason for new consultation in general practice and the second most common reason for antibiotic prescription.<sup>1–3</sup> Children suffer from URTI substantially more often than adults. In a study of 1126 parents, 50% completed a questionnaire demonstrating that 97% of their children had suffered a mean of 7 URTIs in the previous 12 months.<sup>4</sup> Parents regularly use natural health products (NHPs) in the treatment of common childhood ailments, including URTIs.<sup>5,6</sup>

The popularity of herbal medications is increasing in North America, including pediatric use.<sup>7–10</sup> A recent study that we conducted in Canada's largest pediatric emergency department determined

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Dr Vohra developed the study question, designed the study, oversaw its execution, and participated in data analysis and article preparation; Dr Johnston coordinated development of the study protocol, conduct, and analysis and drafted and revised the article; Ms Laycock was the study nurse responsible for recruitment, regular monitoring of participants, and collection of data; Dr Midodzi conducted the analysis and assisted with revisions; and Drs Dhunoo, Harris, and Baydala were responsible for referring participants to the study nurse for recruitment and medical care of the children enrolled. All of the authors read and approved the final article. This trial has been registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (identifier NCT00255307).

### Key Words

ginseng, upper respiratory tract infection, safety, children

### Abbreviations

URTI—upper respiratory tract infection  
NHP—natural health product  
TID—3 times daily  
CARIFS—Canadian Acute Respiratory Infection Flu Scale

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that 41% of surveyed children ( $n = 1804$ ) were current users of NHPs.<sup>11</sup> Similarly, a survey of 142 families in a US pediatric emergency department over a 3-month period suggested that 45% of caregivers gave their child an herbal remedy in the previous year.<sup>9</sup> Regarding pediatric NHP use in the United Kingdom, a face-to-face questionnaire of 500 children or parents/caretakers attending a Cardiff teaching hospital (divisions of endocrinology, gastroenterology, respiratory, and general pediatrics) demonstrated that 38% had used an NHP over the previous year.<sup>10</sup>

Adult evidence suggests that ginseng may be effective in preventing a URTI.<sup>12-15</sup> Ginseng root extracts have long been used in traditional Chinese medicine. "Ginseng" is composed of a number of different species, which belong to the same plant family, the Araliaceae. Korean, Japanese, and American ginseng belong to the genus *Panax*, whereas Siberian ginseng is of the genus *Eleutherococcus*. American ginseng (*Panax quinquefolius*) is currently sold as a health food in Canada and as a dietary supplement in the United States. Such sales amount to more than \$300 million annually in the United States.<sup>12</sup>

Reports of the effectiveness of ginseng are often contradictory,<sup>16,17</sup> perhaps because the chemical content of ginseng root or root extract can differ, depending on the method of extraction, subsequent handling, or even the season of its collection. The multiple physiologic systems affected are thought to be a result of 2 main medicinal fractions derived from ginseng root processing, polysaccharides and ginsenosides, with much of the immunologic activity attributable to the former. Studies have shown that the polysaccharides in ginseng may stimulate the immune system to combat viral infection.<sup>18-22</sup> For instance, an in vitro study using ginseng extract rich in polysaccharides found significantly enhanced production of interleukin 2, tumor necrosis factor  $\alpha$ , interleukin 6, and nitric oxide by mice peritoneal macrophages.<sup>22</sup>

The product that we chose to study for pediatric URTI, a standardized poly-furanosyl-pyranosyl-saccharide extract of North American ginseng, is high in polysaccharides and contains no ginsenosides. The product, COLD-fX (CV Technologies, Inc, Edmonton, Alberta, Canada), is a very popular over-the-counter herbal extract. It is currently the number 1 NHP sold in Canada and was introduced to the US market place in the fall of 2006.<sup>23</sup> Adult safety and efficacy data have been published<sup>13-15</sup>; however, the dose, tolerability, and safety of this product are unknown in children.

## PATIENTS AND METHODS

We conducted a randomized, double-blind dose-finding 3-arm trial (2 dosing schedules of American ginseng extract, with 1 placebo control) in children recruited through 2 teaching hospitals at the University of Alberta. Our objectives were to document the safety and tolerability of 2 weight-based dosing schedules (standard dose versus low dose [half the standard dose]) versus placebo and to establish the SD of the treatment effect of American ginseng extract in reducing severity and duration of URTI in children.

Children aged 3 to 12 years of age were prerecruited between November 2005 and February 2006. Children were ineligible if they had any of the following: (1) routine immunization within 3 months before study enrollment; (2) known hypoglycemia or diabetes; (3) a bacterial illness diagnosed at the same visit (eg, otitis media, pneumonia, etc) that was treated with antibiotic therapy; (4) a malignancy or had undergone treatment for a malignancy in the previous 3 months; (5) known active liver disease (eg, hepatitis); (6) known hypersensitivity to ginseng products; (7) concurrently took warfarin, digoxin, ginseng products, or phenelzine; or (8) a coagulation disorder. Exclusion criteria were based on the current safety profile of ginseng.<sup>12,24-28</sup> If eligible subjects and/or families decided that they wanted to participate in the study, signed assent and/or consent were obtained.

Subjects were instructed to contact the study nurse immediately (within 12 hours), at the onset of a URTI. The common cold or URTI is defined by the International Classification of Health Problems in Primary Care as an illness with evidence of acute inflammation of nasal or pharyngeal mucosa and the absence of other specifically defined conditions, for example, streptococcal pharyngitis, laryngitis, bronchitis, pneumonia, asthma, and hay fever.<sup>29</sup> If the study nurse deemed the symptoms reflective of URTI symptoms, she contacted the pharmacy to randomly assign the subject and prepare an aqueous weight-based supply of ginseng extract or placebo for immediate courier, because subjects were to begin treatment within 48 hours of URTI onset. The pharmacy sent a 3-day supply of active or placebo medication and case report forms for the family to complete.

## Intervention

We used a patented standardized extract from the root of the botanical source material North American ginseng (*Panax quinquefolius* L., family Araliaceae). The standard treatment approach of study product for adult URTI is to take it 3 times daily (TID) for a 3-day course (600 mg TID day 1; 400 mg TID day 2; and 200 mg TID day 3). Based on these data, using an "average" 70-kg adult, a weight-based approach for the standard treatment arm was 26 mg/kg per day on day 1 (maximum: 1800 mg), 17 mg/kg per day on day 2 (maximum: 1200 mg), and 9 mg/kg per day on day 3 (maximum: 600 mg). Children weighing >45 kg who were randomly assigned to the standard dose arm were administered the standard adult dose. The low-dose arm received half the standard dose, that is, 13 mg/kg per day on day 1, 8.5 mg/kg per day on day 2, and 4.5 mg/kg per day on day 3. Children weighing >45 kg who were randomly assigned to the low dose were administered half of the standard adult dose. The placebo arm was also weight based with a corresponding oral aqueous solution. The pharmacy dispensed a 3-day supply of aqueous solution (placebo or active), divided into 3 equal portions to be taken 3 times daily, and labeled the dose for each day accordingly to facilitate ease of administration. The first dose was to be given with breakfast. For children attending school, the parents were instructed to give the child his or her midday dose at 3:30 PM and the third dose just before bedtime.

### Cointerventions and Contamination

Children were free to receive other medications and tests as their primary physician deemed appropriate. The study did not control for the use of acetaminophen, ibuprofen, antibiotics, or the need for blood testing to minimize the impact of the study on the rest of the child's management and care. We recorded all of the medication use to ensure that important covariables were considered in the final analysis. At the start of the treatment, parents were advised not to give their children ginseng for 14 days. They were cautioned that their child may have been randomly assigned to active treatment and they would not want to "double dose" their child.

### Outcome Measures

We documented adverse events and the use of antibiotics and antipyretics for the 14-day period after onset of treatment. Parents were asked open-ended questions about potential adverse effects during telephone follow-ups on days 1, 2, and 3 of treatment and days 10 and 14 posttreatment. Any unfavorable or unintended sign or symptom was documented, whether it was considered to be related and whether it was a symptom of the primary illness or a potential adverse effect of the medication. All of the adverse events were forwarded in a blinded fashion to the primary investigator to be rated as mild (eg, self-resolving), moderate (eg, those that warranted medical evaluation), or serious (eg, those that warranted hospitalization) based on criteria suggested by the National Institutes of Health and Health Canada.<sup>30</sup> The primary investigator was alerted of potentially serious adverse events immediately so that appropriate steps could be taken, including notification of appropriate regulatory bodies. If an adverse event was still ongoing at the end of the study (day 14), the participant's primary pediatrician was contacted to provide ongoing care.

All of the adverse events were assessed by a masked 3-member independent safety committee with expertise in pharmacology, infectious diseases, and randomized, controlled trials to assess causality using an assessment algorithm used by Health Canada and the World Health Organization Collaborating Centre for International Drug Monitoring.<sup>31</sup> Causality was rated as unassessable/unclassifiable, conditional/unclassified, unlikely, possible, probable/likely, or certain. Consensus was reached on all of the ratings.

The SD of treatment effect (ie, the severity and duration of URTI) was measured using the Canadian Acute Respiratory Infection Flu Scale (CARIFS) score. CARIFS was validated to measure symptom severity in children with acute respiratory illness.<sup>1</sup> This 18-item scale covers 3 domains: symptoms (eg, cough), function (eg, play), and parental impact (eg, clinginess).

### Sample Size

As a phase II study, we hoped to randomly assign 20 subjects per arm (20:20:20). Based on best available data, we assumed that 80% of pre-enrolled subjects would proceed to get a URTI during the study period.<sup>32</sup> As such, we

planned to pre-enroll 75 subjects ( $75.0 \times 0.8 = 60.0$ ). Our research nurse split her time between the participating offices, but she only saw the subset of patients who were referred to her for potential study enrollment. Our study numbers reflect how many children developed a URTI as opposed to how many children were seen by our nurse or the recruiting pediatrician offices.

### Random Assignment and Blinding

Eligible children for whom parental consent had been obtained were randomly assigned by the research pharmacy using a computer-based, random-number generator software. Permuted blocked random assignment with block sizes of 3 and an allocation ratio of 1:1:1 (standard dose, low dose, and placebo) was performed. The parents were couriered the study medication in sealed serially numbered opaque bottles according to the random assignment schedule. The placebo solution had the same appearance, volume, weight, texture, odor, and taste as the ginseng products so that the attending physician, parents, child, and study members did not know who was on which medication. The study nurse instructed parents to mix the solution in  $\frac{1}{2}$  cup (125 mL) of apple, orange, or tropical juice and make sure the subjects drank the entire amount. So as to maximize independence from the trial sponsor, study products (both active and placebo) were independently prepared by the university hospital research pharmacy. To test the intactness of the blind at the end of the study, we asked parents to guess which treatment (American ginseng extract or placebo) their child received.

### Analysis

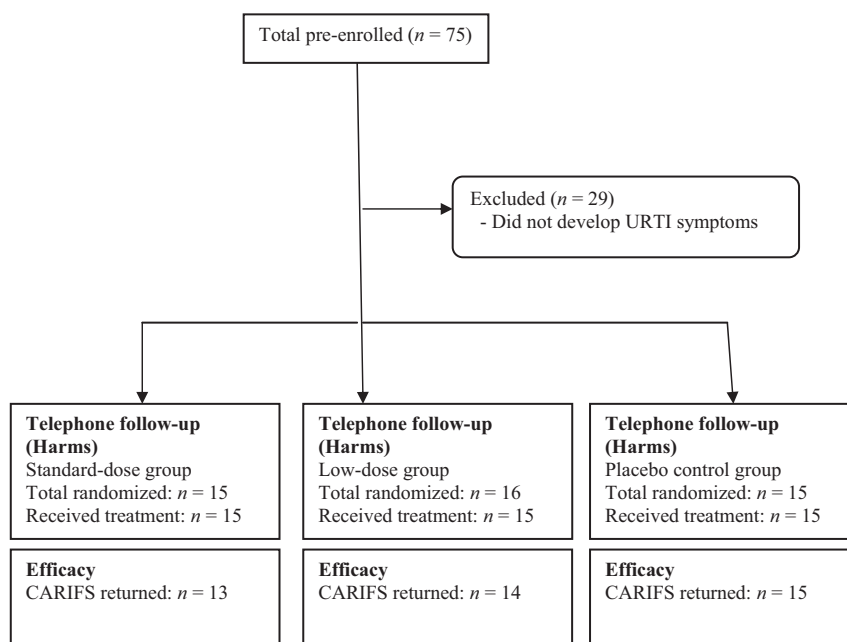
Means and SDs were reported for continuous scaled variables and number and percentages for categorical variables. Proportions of subjects who used antipyretic drugs were compared across groups by using  $\chi^2$  tests. A generalized estimating equation method was used to adjust for correlated pre and post use of antipyretic medications comparison among the treatment arms. Responsiveness (ie, time until CARIFS dropped below one fourth of the baseline score) was constructed by using box and whisker plots for the time until CARIFS dropped below one fourth of the baseline score by using SPSS 14.0 (SPSS Inc, Chicago, IL).

### RESULTS

We pre-enrolled 75 subjects, of which 46 (61%) developed a URTI and were randomly assigned. One subject withdrew from the low-dose arm before beginning the intervention, leaving 45 subjects for evaluation (15:15:15; see Fig 1). All of the subjects contacted the research nurse within 12 hours of symptom onset, and of 45 subjects who began treatment, 44 did so within 24 hours (the remaining subject began treatment within 48 hours). Baseline demographics were comparable across treatment arms with regards to age, weight, height, gender, household smoking status, and medication or NHP use (see Table 1).

No serious adverse events were reported. Thirty-one

FIGURE 1  
Flowchart of all study subjects.



subjects reported 51 adverse events, with 14 subjects experiencing  $\geq 2$  adverse events. The difference in the number of subjects with adverse events among each of the 3 treatment arms was nonsignificant (standard dose: 60% [9 of 15], low dose: 80% [12 of 15], placebo: 67% [10 of 15];  $P = .48$ ; see Table 2). The mean number of adverse events per group was 0.93 (14 of 15) for the standard dose, 1.33 (20 of 15) for the low dose, and 1.13 (17 of 15) in the placebo group. Of the 51 adverse events, the masked primary investigator (Dr Vohra) rated 43 as mild (ie, self-resolving) and 8 as moderate (ie, required medical attention) with a significant difference across groups ( $P = .02$ ). Two moderate adverse events occurred in the low-dose group: 1 subject with

secondary bacterial throat infection required antibiotics, and a second subject experienced prolonged fever. Six moderate events occurred in the placebo group in 3 subjects: 1 with fever, headache, and vomiting; 1 with fever and leg pain; and 1 with irritability. No moderate adverse events occurred in the standard-dose group.

Eleven adverse events were classified by a blinded expert subcommittee as possibly related to the intervention, with a nonsignificant difference across groups ( $P = .95$ ). The nature of these events were as follows: in the standard-dose group, 2 subjects experienced fever and 1 subject reported irritability; in the low-dose group, 2 subjects experienced fever, 1 subject experienced a headache, and 1 subject reported a stomach ache; and in

TABLE 1 Baseline Demographics, Use of NHPs, Medications

Variables	Standard Dose (N = 15)	Low Dose (N = 15)	Placebo (N = 15)	Overall (N = 45)
Demographics				
Age, mean (SD), y	4.4 (1.4)	5.5 (2.3)	5.0 (2.2)	5.0 (2.0)
Weight, mean (SD), kg	19.5 (4.6)	22.7 (8.5)	19.4 (4.3)	20.5 (6.2)
Height, mean (SD), cm	105.8 (10.8)	116.1 (17.7)	108.4 (12.2)	110.3 (14.4)
Male gender, n (%)	7 (46.6)	7 (46.6)	10 (66.6)	25 (55.5)
Smoking in household, n (%)	3 (20.0)	0 (0.0)	2 (13.3)	5 (11.1)
Medication use				
Previous use (<3 mo)				
Multivitamins, n (%)	6 (40.0)	6 (40.0)	8 (53.3)	20 (44.4)
NHPs, n (%)	1 (6.6)	1 (6.6)	2 (13.3)	5 (11.1)
Antipyretics, n (%)	7 (46.6)	5 (33.3)	6 (40.0)	18 (40.0)
Mean (SD), d <sup>a</sup>	21.6 (22.2)	24.2 (14.9)	25.5 (21.9)	23.6 (19.2)
Other medications, n (%)	3 (20.0)	5 (33.3)	1 (6.6)	9 (20.0)
Baseline (at randomization)				
Multivitamins, n (%)	3 (20.0)	1 (6.6)	0 (0.0)	4 (8.8)
NHPs, n (%)	0 (0.0)	0 (0.0)	2 (13.3)	2 (4.4)
Antipyretics, n (%)	1 (6.6)	2 (13.3)	3 (20.0)	6 (13.3)
Other medications, n (%)	3 (20.0)	3 (20.0)	2 (13.3)	8 (17.7)

<sup>a</sup> Mean number of days since last dose.

**TABLE 2 Adverse Events**

Variable	Standard (N = 15)	Low (N = 15)	Placebo (N = 15)
Symptoms and signs, <i>n</i> (%)	9 (60.0)	12 (80.0)	10 (66.7); NS
Headache, <i>n</i>	1	2	2
Intermittent fever, <i>n</i>	7	8	5
Irritability, <i>n</i>	2	1	3
Low energy, <i>n</i>	1	2	2
Not sleeping well, <i>n</i>	0	1	1
Stomach pain, <i>n</i>	1	1	0
Bleeding nose, <i>n</i>	0	1	0
Earache, <i>n</i>	1	0	0
Leg pain, <i>n</i>	0	0	1
Anorexia, <i>n</i>	0	0	1
Rash, <i>n</i>	0	1	1
Sinus infection, <i>n</i>	0	1	0
Strep throat, <i>n</i>	0	1	0
Vomiting, <i>n</i>	0	0	1
Vomiting with cough, <i>n</i>	1	1	0
Mean No. of adverse events, <i>n/N</i> (mean)	14/15 (0.93)	20/15 (1.33)	17/15 (1.13)
Committee results, overall			
Severity ( $P = .018$ )			
Mild, <i>n/N</i> (%)	14/14 (100)	18/20 (90.0)	11/17 (64.7)
Moderate, <i>n</i>	0	2	6
Severe, <i>n</i>	0	0	0
Degree of association ( $P = .945$ )			
Unclassified/unassessible, <i>n</i>	0	0	0
Unlikely, <i>n/N</i> (%)	11/14 (78.6)	17/20 (85.0)	13/17 (76.5)
Possible, <i>n/N</i> (%)	3/14 (21.4)	4/20 (20.0)	4/17 (23.5)
Probable, <i>n</i>	0	0	0
Certain, <i>n</i>	0	0	0

$\chi^2$  statistics were used for calculating *P* values. NS indicates not significant.

the placebo group, 2 subjects reported irritability, 1 subject reported low energy, and 1 subject reported loss of appetite.

Forty-two of 45 subjects returned their CARIFS forms (see Appendix). Because there is no “normal” score for CARIFS, subjects were evaluated according to their baseline score and time to drop to below one quarter of the baseline score.<sup>1</sup> The SDs of treatment effect involving the mean length of time in days from treatment onset to when symptoms resolved were as follows: 1.5 (1.6) for standard treatment, 1.9 (1.5) for low dose, and 1.9 (2.2) for placebo. More than 90% of children in all 3 of the treatment groups demonstrated recovery by day 4 (see Fig 2). Based on our pilot data, if one looked at a minimal clinically important difference of 30% improvement in the time to reach one quarter of the baseline CARIFS score, then a 2-arm parallel group randomized, controlled trial of ginseng versus placebo would need 96 subjects (48 per arm,  $\alpha$  set at .05 and 80% power, and a 2-sided test).

Subjects in the standard arm were the most symptomatic at study entry, with highest mean body temperature and highest CARIFS score. Despite this, subjects in the standard arm had symptoms resolve as quickly as those in the low-dose arm (see Table 3). Furthermore, antipyretic use was highest in the low-dose group ( $P = .48$ ). The use of cold and/or flu remedies, antibiotics, and

asthma medications did not differ between arms (see Table 4).

All of the subjects who began treatment ( $n = 45$ ) took the intervention each of the 3 days. Over the 3-day dosing regimen, 43 subjects took all 9 of the doses, whereas 2 subjects took 8 doses (1 subject in the standard group and 1 in the placebo group each missed a dose). There was no relationship between what treatment parents thought their child was on and actual treatment group assignment ( $P = .16$ ).

## DISCUSSION

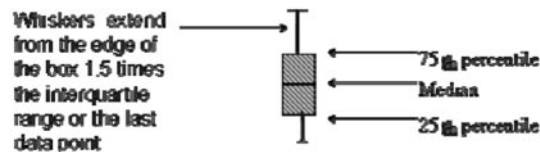
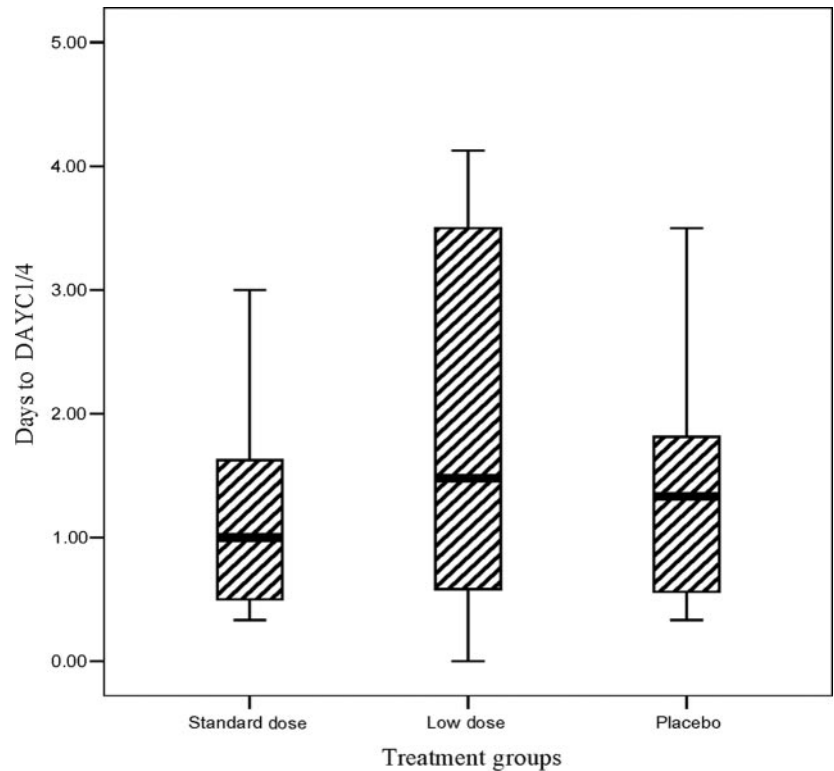
Despite extensive efforts and considerable expense, there is no known effective cure for the common cold. Ginseng, a popular herbal remedy, is purported as effective in the prevention of adult URTI but has not had the benefit of rigorous evaluation in children.<sup>12–15</sup> To our knowledge, no published study has evaluated ginseng for pediatric URTI. As a phase II dose-finding study, our goal was to determine which dose was safe and well tolerated in young children. Weight-based dosing adapted from standard adult doses was statistically indistinguishable from low dose or placebo with regard to adverse event profile. The overall compliance suggests that there were no dosing-related problems across arms and that the standard dose was well tolerated.

No single method of determining drug dose or clearance is suitable for all products or age groups. Because dosing requirements can vary widely with age, we first chose to omit neonates, infants, and pubertal children. We then modified “Clark’s rule” (child’s dose = child’s weight [kilograms]  $\times$  adult dosage divided by 70), such that only children weighing  $>45$  kg (ie, the weight of a small adult) would be exposed to an adult dose.<sup>33,34</sup>

Subjects in the standard arm were the sickest, as measured by their baseline CARIFS score, yet they recovered as quickly as the subjects in both other arms. This result may have been influenced by the use of other over-the-counter medications in the placebo group. In particular, 2 subjects who were randomly assigned to placebo used oil of oregano, which has been historically used for coughs and colds (its chief component, carvacrol, has been demonstrated to have antimicrobial properties).<sup>35</sup> Although the difference in NHP use across arms was not significant, future investigations should caution participants to avoid using other NHPs during the study period to avoid potential confounding. In addition, whereas the use of asthma medications was similar across groups at baseline, there was a trend to increased use during treatment in the standard dose arm, although this difference was not statistically significant ( $P = .27$ ; see Table 4). According to their baseline CARIFS score, subjects in the standard arm were the most ill, which may have accounted for their higher use of asthma medications. Although this difference was not statistically significant, we encourage future investigations of ginseng to include specific measurement of asthma status as part of their prospective evaluation.

Because NHPs have been exempt from the methods standard to drug development, there is often an unac-

FIGURE 2  
Box plots of responsiveness of the CARIFS score to treatment ( $P$  [test of mean difference] = .717).



ceptably high degree of product heterogeneity, both quantitative and qualitative, which has implications for biological function and efficacy.<sup>36–38</sup> This heterogeneity has been a major limiting factor in the critical evaluation of herbal remedies.<sup>38</sup> Heterogeneity can also affect safety in that many reports of toxicity originate in those countries that lack medicolegal regulation of ginseng use.<sup>39</sup> In contrast, reports of toxicity are rare in Germany and other European countries in which ginseng is medically prescribed and used in recommended doses. We over-

came this limitation by using American ginseng extract that has been standardized chemically and has demonstrated efficacy in adult clinical trials.<sup>13–15</sup> Our data confirm this safety profile when ginseng is prepared in a standardized fashion.

We report 1 of the few phase I or II trials of NHPs in children. A Medline (1950 to January 2007 week 2) and EMBASE (1988 to January 2007 week 2) search using terminology relating exclusively to phase I and II trials, combined with synonyms for NHPs, revealed only 7 citations exclusively about children. This is especially concerning given that current estimates suggest that 41% to 45% of children in Canada and the United States use NHPs.<sup>9,11</sup> As is routine in the evaluation of conventional pharmaceuticals, rigorous stepwise evaluation (phase I to phase III) may help improve NHP research. For example, the pediatric literature is ripe with examples of large expensive phase III trials of NHPs with negative results.<sup>32,40–42</sup> These trials have been criticized for inappropriate dosing, inappropriate inclusion and/or exclusion criteria, and a significantly higher rate of adverse effects in the treatment versus placebo group.<sup>40,41,43</sup> It is preferable to ensure adequate product characterization and formal evaluation of dosing and safety before proceeding to evaluate clinical efficacy. Investigators and funding agencies will thereby be less likely to

TABLE 3 Clinical Outcomes

Variable	$P$	Standard ( $N = 13$ )	Low ( $N = 14$ )	Placebo ( $N = 15$ )	Overall
Time from symptoms onset to start of treatment, mean (SD), h	.835	12.5 (6.9)	10.8 (7.5)	10.8 (11.7)	11.4 (8.7)
Body temperature baseline, mean (SD), °C	.242	37.6 (0.75)	36.9 (0.74)	36.9 (0.91)	37.1 (0.83)
CARIFS score at baseline, mean (SD)	.070	13.9 (7.6)	8.7 (5.7)	9.2 (5.3)	10.5 (6.5)
Length of time from treatment to when symptoms resolved, mean (SD), d	.762	1.5 (1.6)	1.9 (1.5)	1.9 (2.2)	1.8 (1.7)

**TABLE 4 Other Medication Used During Treatment Period**

Medication Use	<i>P</i> <sup>a</sup>	Standard, <i>n</i>		Low, <i>n</i>		Placebo, <i>n</i>	
		Current	Previous	Current	Previous	Current	Previous
Overall		36	6	42	9	30	5
Cold/flu remedies	.80	7	3	9	5	9	2
Antibiotics	.66	5	0	3	0	0	0
Asthma medications	.27	18	1	8	0	4	0
Antipyretics	.48	6	2	17	4	6	2
Other		0	0	5	0	11	1

<sup>a</sup> *P* values indicate differences in the treatment groups for current use of medication after adjustment for previous use of medications at baseline. Generalized estimating equation methods were used to adjust for correlated outcomes.

waste valuable resources and expose children to potentially harmful or ineffective NHP doses in large clinical trials that lack adequate justification.

Compared with other herbal products, evidence of the safety of ginseng has been extensively reported in adults. In particular, a systematic review of adverse effects of *Panax ginseng*; Korean, Chinese, Oriental, and/or red ginseng (which contain ginsenosides); or ginseng combined with other products has been reported involving a total of 146 clinical trials and 27 case reports.<sup>24</sup> Clinical trials have reported gastrointestinal disturbances, nervousness, insomnia, and the potential for ginseng to lower fasting blood glucose in noninsulin dependent diabetic patients,<sup>24,27</sup> whereas case reports collected by the World Health Organization Collaborating Centre for International Drug Monitoring Database have reported the potential for hepatitis and prothrombin dysregulation.<sup>24</sup> Although no pharmacokinetic studies of potential drug interactions with ginseng have been conducted in children,<sup>44</sup> herb-drug interactions between American ginseng and warfarin,<sup>29</sup> Siberian ginseng, and digoxin<sup>26</sup> and an unknown ginseng product and phenelzine have been reported.<sup>25</sup>

The nature, severity, and attribution of harms, however minor, are always important to capture in clinical trials. In the case of treating the common cold, a self-limiting illness, the minimal clinically important benefit may not be as important as the minimal clinically important harm to families and clinicians, especially with respect to their evaluation in children.<sup>45</sup> The reporting of harms of conventional pharmaceutical trials has often been unclear or inadequate.<sup>46</sup> To explore this issue related to ginseng products, we searched for randomized, placebo-controlled trials of ginseng published between 2002 and January 2007 and documented the quality of adverse event reporting. Our search yielded 15 randomized, placebo-controlled trials, none reporting any serious adverse events. However, the overall quality of reporting was poor, because only 1 trial reported using standardized adverse event definitions or applied attribution and/or causation criteria to each of the adverse events reported,<sup>13</sup> and only 5 of the 15 trials reported active monitoring and follow-up for adverse events, as recommended by the CONSORT (Consolidated Standards of Reporting Trials).<sup>13,14,47–51</sup> We think that future trials must improve the quality of adverse event reporting so that families and clinicians can make informed decisions about NHP use for self-limited conditions.

Our study had a number of strengths and limitations. Almost all of the subjects began treatment as recommended (within 24 hours of illness onset), blinding was intact, there was high compliance with the study intervention, and the degree of association between adverse events and ginseng extract was rated by an independent blinded committee with relevant expertise. Our study is limited by the concomitant use of NHPs by study participants. This could confound interpretation of the treatment effect. We recommend that future studies of NHPs refrain from allowing concurrent use of other NHPs. Although our study achieved its primary objective, it was not powered to detect a difference in treatment effect.

## CONCLUSIONS

Although the published literature has reported evaluation of the prophylactic use of American ginseng extract,<sup>13–14</sup> it is marketed as an over-the-counter treatment for the common cold.<sup>52</sup> As the first pediatric study evaluating its safety, we felt it was more appropriate to evaluate short-term use of ginseng extract in children for URTI treatment before exposing a cohort of children to long-term daily use for months for URTI prophylaxis. This phase II study was designed to generate safety data and to establish the SD of treatment effect for future sample-size calculations. Our data support that standard weight-based approach to dosing ginseng is appropriate for phase III evaluation of efficacy for the treatment of pediatric URTIs. Given the growing body of evidence suggesting that ginseng may be an effective URTI prophylaxis, additional studies examining the safety profile of chronic daily use of ginseng in children also seem worthwhile.

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**APPENDIX Parent CARIFS diary**

Day \_\_\_\_\_ Subject No. \_\_\_\_\_  
 Time \_\_: \_\_ : \_\_  am  pm Temperature: \_\_. \_\_ °C  
 h h m m

	No Problem	Minor Problem	Moderate Problem	Major Problem	Don't Know or Not Applicable
Poor appetite					
Not sleeping well					
Irritable, cranky, fussy					
Feels unwell					
Low energy, tired					
Not playing well					
Crying more than usual					
Needing extra care					
Clinginess					
Headache					
Sore throat					
Muscles aches or pains					
Fever					
Cough					
Nasal congestion, runny nose					
Vomiting					
Not interested in what's going on					
Unable to get out of bed					

**Safety and Tolerability of North American Ginseng Extract in the Treatment of Pediatric Upper Respiratory Tract Infection: A Phase II Randomized, Controlled Trial of 2 Dosing Schedules**

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