Applied nutritional investigation

Effect of vitamin A, vitamin A plus iron and multiple micronutrient-fortified seasoning powder on infectious morbidity of preschool children

Ke Chen Ph.D. a,b, Xuan Zhang Ph.D. c, Ting-yu Li M.D. a,* Li Chen Ph.D. c, Xiao-ping Wei M.D. a, Ping Qu M.D. a, You-xue Liu Ph.D. a

a Ministry of Education Key Laboratory of Children Development and Disorders, Children's Nutritional Research Center, Children's Hospital, Chongqing, People's Republic of China
b Department of Child Health Care, Chengdu Maternal and Children's Health Care Hospital, Chengdu, Sichuan Province, People's Republic of China
c Department of Child Health Care, Children's Hospital, Chongqing Medical University, Chongqing, People's Republic of China

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ABSTRACT

Objective: Improvement of hemoglobin and serum retinol and facilitation of the mobilization of iron storage were achieved with a multiple-micronutrient–fortified diet in preschoolers for 6 mo in a suburb of Chongqing, China. We investigated whether fortification with multiple micronutrients in a diet for preschool children results in changes in children's infectious morbidity compared with diets fortified solely with vitamin A and with vitamin A plus iron.

Methods: From December 2005 to June 2006, 226 2- to 6-y-old preschool children were recruited from three nurseries randomly assigned to three different fortified-diet groups for 6 mo. Group I was fortified with vitamin A; groups II and III were fortified with vitamin A plus iron and vitamin A plus iron, thiamine, riboflavin, folic acid, niacinamide, zinc, and calcium, respectively. The secondary functional outcomes, morbidity of diarrhea and respiratory infection, were collected during supplementation.

Results: The groups were comparable concerning compliance and loss to follow-up. There was evidence of a lower incidence rate of respiratory-related illnesses, diarrhea-related illness, fewer symptoms of runny nose, cough, and fever, and shorter duration of respiratory-related illnesses and cough for children in group III compared with children in groups I and II. However, there was no significantly or clinically important difference between children in groups I and II.

Conclusion: The beneficial effects on infectious morbidity over 6 mo, in addition to some biochemical improvements, highlight the potential of this micronutrient-fortified seasoning powder supplied in a diet for preschool children.

Introduction

Defense against infectious disease is a matter of the highest importance for the health and development of tropical populations. Despite the high prevalence of vitamin A deficiency and iron deficiency, several studies have addressed the issue that supplementation of vitamin A [1,2] and/or iron [3,4] can significantly improve the insufficient status and simultaneously decrease the mortality and/or morbidity of infectious diseases.

However, worldwide, micronutrient deficiencies, particularly involving iron, zinc, folic acid, vitamin B12, and vitamin A, among others, remain major problems in many regions [5]. In developing countries, children represent a vulnerable population who may have multiple micronutrient deficiencies, especially preschool children, because of the same causative factors that are responsible for the insufficiency of more than one essential micronutrient.

Micronutrient deficiencies can have adverse health consequences, such as impairments in growth, neurobehavioral dysfunctions, and defective immunity [6], which not only contribute to delays in growth and development but also are important factors in the transmission and progression of infectious diseases, increases in morbidity and mortality, and decreases in intellectual potential [7–10]. Therefore, decreasing...
the prevalence of micronutrient deficiencies is a highly priori-
tized strategy for many health policy makers in the governments
of these countries.

In response to these strategies about the prevention of coex-
isting micronutrient deficiencies in children in developing
countries, targeted multiple micronutrient fortification is used in
a variety of vehicles [11–15]. This is a relatively new approach, and
only a few studies have examined its efficacy on functional health
outcomes, such as improvements in growth, cognitive function,
and decreases in infectious illnesses, and on biochemical indices.

In fact, several simple fortification methods have been developed
in China, whereas no foods fortified with multiple
micronutrients are currently available [16–18]. From December
2005 to June 2006, we performed a supplementary program to
evaluate the effectiveness of different combinations of multiple
micronutrients on nutritional status in a preschool population
[19]. We demonstrated in a randomized, controlled trial that
a seasoning powder package, consisting of single-dose sachets
(resembling small packets of sugar or artificial sweetener) con-
taining micronutrients in powder form that are easily sprinkled
onto foods prepared in nurseries, with eight micronutrients
incorporated into a nursery-food program, decreased the prev-
ance of anemia and vitamin A deficiency and improved iron
metabolic status and anthropometric growth. Any homemade or
untorted food can be thus fortified by such a package to
administer once-a-day doses of micronutrients.

Although improvements in these biochemical outcomes are
promising, improvements in functional health outcomes are also of
key importance. In this publication we report the efficacy of
the intervention on outcomes of infectious morbidity, such as
diarrhea and respiratory infection, after 6 mo supplementation.

Materials and methods

Details of the supplementary field trial design, including inclusion and
exclusion criteria, were described in a previous publication [19].
The enrollment and research plans were reviewed and approved by the
institutional ethical committee of the Children’s Hospital of Chongqing Medical
University in Chongqing, China. This supplementation program was performed in
the Banan District of Chongqing, China, from December 2005 to June 2006. The
Banan District is a suburb of Chongqing with a middle-class socioeconomic status
and was previously investigated for child nutrition supported by the Sight and
Life International Vitamin A Research Foundation (Holland).

The calculation of sample size was described previously [19]. Briefly, our
power calculation was based on detecting differences in the longitudinal prev-
ance of diarrhea (log-transformed) among three groups. We simulated pub-
lished values of the longitudinal prevalence of diarrhea, log-transformed these
values (using a natural logarithmic scale), and estimated the standard deviation
(STD; 0.5; placebo group). Because a 5% absolute increase in the longitudinal
prevalence of diarrhea is associated with a 17% increased risk of mortality [20],
we considered a 5% difference in the longitudinal prevalence of diarrhea among
groups to be clinically meaningful. Therefore, we estimated that 30 children per
group would ensure a power of 90% (α = 0.05) to detect “between-group”
differences for the longitudinal prevalence of diarrhea (log-transformed).
To allow for attrition over the duration of the study, we initially managed to recruit
about 100 children per group. Thus, using infectious illness as a secondary
outcome, we also had sufficient power to evaluate the hypothesis. However, the
primary outcome measurements including analysis indices before and after
supplementation were obtained from 226 preschool children due to the unexpectedly,
relatively high dropout rate for involvement in the present trial.

More than 300 preschool children 2 to 6 y old were randomly recruited from
15 nurseries or kindergartens in this region. The eligibility criteria for partici-
patation were 1) apparent health, 2) a hemoglobin (Hb) concentration >60 g/L, 3)
a C-reactive protein level <10 mg/L, 4) parental or guardian approval to partic-
ipate in all aspects of the study, and 5) parental/guardian agreement to avoid the
additional use of vitamin and mineral supplements during the investigation.
Children with evidence of recent acute or chronic illnesses and/or a Hb level <60
mg/L were not included in the study and were referred to the local medical center
for treatment. Two of the authors explained the objectives and procedures of the
study to the parents/guardians of the enrolled children, and informed written

Intervention

This study used a fortified seasoning powder that was added directly to
porridge, bean milk, soup, or noodles after cooking. The powders, with maltose
used as filler, were indistinguishable in taste, color, and packaging, except for
coded numerical labeling. Each serving of the fortified seasoning powder
provided 100% of the recommended daily intake (set by the Chinese Nutrition
Society). Package I contained powder with vitamin A (500 μg as dry vitamin A
acetate) supplements, package II contained vitamin A and iron (12 mg as ferric
sodium edentate), and package III contained powder supplemented with vitamin
A, iron, thiamine (0.7 mg as thiamine mononitrate), riboflavin (0.7 mg), folic acid
(0.2 mg), niacinamide (7 mg), zinc (12 mg as zinc oxide), and calcium (800 mg as
calcium carbonate). These premixed powders were provided by the DSM
Company (Shanghai, China; premix code VR01932321).

The study was designed as a double-blind, randomized trial. With the help of
child health care workers, the children in each nursery were randomly recruited into
groups I, II, and III, which were given fortified seasoning powder packages I,
II, and III, respectively, for 6 mo. No intervention took place during school holi-
days or public holidays, and the packages were provided for a total of 120 school
days (equivalent of 24 wk).

Food prepared with seasoning powder was delivered to each child at
lunchtime or afternoon snack time, 5 d/wk, during the study period. The chefs in
the nurseries received additional training about preparing the foods with the
different fortified seasoning powders. The enrolled children received their
respective foods under the supervision of caregivers for the designated groups.

Compliance

Compliance was monitored using records of adherence in which teachers recor-
ded whether the child consumed their assigned “confidential food” (sometimes
of packages by classmates, the three groups were physically separated by being
moved to opposite corners of the classroom. Distribution and consumption of the
package took place under close supervision; children were not allowed to leave
the classroom or return to their original seats before they had finished eating
that package. Information on the acceptability of the seasoning powders was
obtained by a short questionnaire administered at the 6-mo assessment.

At baseline, morbidity data were based on self-reported infection status
(respiratory, diarrhea, and parasitic) obtained through personnel
interviews with the parents or caregivers of the children in the previous 2 wk.
Information was also collected at this baseline visit regarding the number of
household members and their ages, education levels, income, household
construction materials, the source and quality of household water, the type of
household sanitation facilities, and household possessions. The mothers or child
caretakers were also interviewed regarding the dietary patterns of the children.
A previously validated questionnaire was used to collect these data by project
personnel who had received training in its application.

At the same time, parents or guardians were also informed about the stan-
dsardized checklist that would be used by the teachers to record the morbidity
data throughout the randomized-controlled trial and were requested to inform
the teacher if their child had experienced any of the symptoms on the stan-
cardized check list. The symptoms recorded were respiratory-related illnesses
(runny nose, cough, and sore throat), fever, skin rash, other illnesses, and
diarrhea-related illnesses (diarrhea, vomiting, nausea, and stomach pain); Diar-
rrhea was defined as the passage of loose or liquid stools and a high stool
frequency (i.e., >3 stools/d). A morbidity episode was defined as an event of
morbidity symptoms with 3 illness-free days between events. If a child was
absent from school, then the reason for the absence was obtained retrospectively
from the mother, guardian, or child and recorded on the standardized checklist
by the teacher. Morbidity data were collected on each school day by the teacher
for a maximum of 120 weekdays and retrospectively for about 60 weekend days
and several public holidays.
Anthropometric measurements

Anthropometric examinations in each nursery were conducted by the same trained anthropometrist (a total of three) from the Chongqing Children’s Hospital at baseline and follow-up (6-mo) time points using standardized techniques to eliminate intraexaminer error. Duplicate measurements were performed for all participants. The interexaminer coefficient of variation of weight and height for each examiner in groups I, II, and III was less than 5%. Weight was recorded using a weighing scale (100 Med, Beijing, China) to the nearest 100 g with subjects in minimum clothing and bare feet. Similarly, height (>3 y old)/length (<3 y) was measured in the standard position by the same standing scale (100 Med) or a supine position by a supine scale (Haode, Guangzhou, China) to the nearest 0.1 cm. By using reference data from the US National Center for Health Statistics and World Health Organization (WHO; 2005), the 2 scores were calculated for height for age, weight for height, and weight for age. All indices were computed using Anthro (2005) for the personal computer, as recommended by the WHO (http://www.who.int/childgrowth/software/en/).

Blood samples and biochemical measurement or assessment

At the beginning and end of the 6-mo period, two blood samples (about 3 mL) were collected by venipuncture of an antecubital vein from each subject before breakfast. One milliliter was drawn into a container containing heparin to measure Hb by the hemoglobin cyanide method [21] (Maker, Chengdu, China). The interassay variation was lower than 5% and the intra-assay variation was lower than 10%. The remaining blood was centrifuged at 3000 × g for 5 min at room temperature. The serum samples were immediately stored at −20 °C to prevent micro-hemolysis and separated within 5 h. The centrifuged serum samples were divided into aliquots and immediately transported to the laboratory and stored at −20 °C. The serum samples prepared for retinol measurement were protected from light. The concentrations of serum ferritin [22] were measured using a commercial enzyme-linked immunosorbent assay (Sunbiote, Shanghai, China).

Serum retinol concentration was determined by using high-performance liquid chromatography according to the method of Harirahan M et al. [23], with slight modification. Briefly, retinol was extracted with hexane after deproteinization with ethanol containing retinyl acetate as the external standard. The blood samples were immediately stored at 4 °C to prevent micro-hemolysis and separated within 5 h. The centrifuged serum samples were divided into aliquots and immediately transported to the laboratory and stored at −20 °C. The serum samples prepared for retinol measurement were protected from light. The concentration of retinol was determined with a spectrophotometer (Waters 2487 Dual λ Absorbance Detector, Waters Breeze) at 315 nm. Duplicate analyses were performed on one-tenth of the samples and the estimated variability was 0.02 μmol/L. Three control serum samples with low (0.70 μmol/L), medium (1.40 μmol/L), and high (2.79 μmol/L) concentrations of serum retinol were supplemented with a standard retinol solution (Sigma Chemical Co., St. Louis, MO, USA) in the pooled serum. The between-day coefficients of variation for low, medium, and high concentrations were 5.68%, 3.16%, and 1.85%, respectively. The experienced examiners in the Pediatric Laboratory of Chongqing Medical University measured all biochemical indices.

Statistical analysis

Using the Kolmogorov-Smirnov goodness-of-fit test, the distribution of each set of data was tested for normality before analysis. Data were presented as mean ± SD for normally distributed variables or median (25th, 75th percentiles) for abnormally distributed variables; when necessary, data were normalized using natural log-transformations. Tests of significance were two-tailed and P < 0.05 was considered statistically significant. Paired Student’s t-tests were used to compare paired data with normal distribution and homogeneous variance in the before–after intervention pairs of each group, and paired Wilcoxon sign-rank test was used for abnormally distributed data. Chi-square test was used for baseline and follow-up (6-mo) time points using standardized techniques to among multiple groups. To compare the different effects among the three interventions, we performed multiple comparisons of the changes of parameters over the 6 mo of intervention (P < 0.05 set for statistical significance) with the Student-Newman-Keuls test (normal and homogeneous data) or Student- Newman-Keuls rank test (abnormal data). For the Student-Newman-Keuls test or rank test, the Student-Newman-Keuls grouping letters were provided.

Multiple linear regression models were used to estimate the effectiveness of the intervention for continuous outcomes. In these models, the design strata (age in months, sex, and school) were included as explanatory variables. School was included as a fixed effect. Adjustment for baseline of the outcome using regression analysis is generally the preferred approach because of beneficial statistical properties.

Negative binomial regression was used to estimate the effectiveness of the intervention for morbidity episodes. Negative binomial regression was used in preference to Poisson’s regression because there was evidence of overdispersion in morbidity episodes. These models were also adjusted for the covariates. Durations of respiratory-related illness, runny nose, and cough were compared among groups using multiple linear regressions. Only these morbidity outcomes were analyzed because there was a reasonable number of children who had these illnesses. For each child, an average duration of illness was calculated as the total number of days with the illness divided by the number of episodes of the illness. These outcomes were natural log-transformed to decrease heteroscedasticity of the residuals. From these models, the exponential of the estimated intervention effect provides a ratio of the geometric mean of the outcome in the fortified group to that in the unfortified group. Participants were analyzed as randomized. No imputation was performed.

Data were analyzed using SAS 9.0 for Windows (SAS Institutes, Cary, NC, USA).

Results

The flow of children through each stage of the trial and the final number analyzed for the primary outcome, anemia, were reported previously [19]. In brief, 318 preschool children from three different nurseries were randomly selected to participate. Among the children, about 20 were excluded (4 for Hb level < 10 g/L, 15 for C-reactive protein level > 10 mg/L, and 11 for parents refusing permission), and 282 children met the study inclusion criteria (85 for group I, 96 for group II, and 101 for group III). About 20% (56 of 282) dropped out during the course of the study. The dropout numbers were 24 (4 for blood drawing failure and 20 for moving during the trial) for group I, 25 (4 for blood drawing failure and 21 for moving during the trial) for group II, and 7 (1 for blood drawing failure and 6 for moving during the trial) for group III. Thus, primary outcome measurements including analyses of micronutrient status of blood and anthropometric indices were obtained from 226 preschool children (61, 71, and 94 in groups I, II, and III, respectively). Retrospective data documented daily by caregivers indicated about 95% compliance, indicating that at least 95% of the preschool children took the seasonal powder daily during the study period.

The age of the children in the study was 4.0 ± 0.85 y (mean ± SD). Approximately 51% of the children were female. For each group, the age (mean ± SD) and ratio of boys to girls were 4.2 ± 0.79 y and 30 to 31, 3.9 ± 0.72 y and 32 to 39, and 4.0 ± 0.91 y and 50 to 44 in groups I, II, and III, respectively.

Details of the biochemical and anthropometric statuses of the children at baseline and after intervention were presented previously [19]. At baseline, there was no significant clinical difference in age, sex proportion, anthropometric measurements, and health status and sociodemographic variables among the intervention groups (Table 1). Moreover, there was no difference in infectious morbidity for the children in each supplementary group who dropped out (data not shown).

Measurements of compliance

In total, about 91.6% of the preschool children received all 120 doses, 3.1% received at least 80 doses, 3.5% at least 40 doses, and 1.8% received no more than 40 doses. The different proportions of children receiving doses during the intervention were not significant among groups (Table 2). The mean number of supplements taken per child was 115.3 and was similar in all groups; 112.5 supplements were taken in group I, 117.5 in group II, and 116.0 in group III (Table 2). No adverse events were reported during the study.
Table 1
Sociodemographic, anthropometric, and biochemical characteristics of the three intervention groups at baseline

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n = 61)</th>
<th>Group II (n = 71)</th>
<th>Group III (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>4.2 ± 0.79</td>
<td>3.9 ± 0.72</td>
<td>4.0 ± 0.91</td>
</tr>
<tr>
<td>Boys/girls¹</td>
<td>30/31</td>
<td>32/39</td>
<td>50/44</td>
</tr>
<tr>
<td>At least high school education in caregivers¹</td>
<td>28 (45.9)</td>
<td>33 (46.5)</td>
<td>43 (45.7)</td>
</tr>
<tr>
<td>Monthly family income¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1500 yuan</td>
<td>14 (22.9)</td>
<td>17 (23.9)</td>
<td>23 (24.9)</td>
</tr>
<tr>
<td>1500–3000 yuan</td>
<td>17 (27.9)</td>
<td>22 (31.0)</td>
<td>25 (26.6)</td>
</tr>
<tr>
<td>3000–5000 yuan</td>
<td>15 (24.6)</td>
<td>14 (19.7)</td>
<td>26 (27.7)</td>
</tr>
<tr>
<td>&gt;5000 yuan</td>
<td>15 (24.6)</td>
<td>18 (25.4)</td>
<td>20 (20.8)</td>
</tr>
<tr>
<td>Use of vitamin/mineral supplement before trial¹</td>
<td>8 (13.1)</td>
<td>6 (8.5)</td>
<td>11 (11.7)</td>
</tr>
<tr>
<td>Illness in previous month¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (6.5)</td>
<td>4 (5.6)</td>
<td>5 (5.3)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>22 (36.1)</td>
<td>27 (38.0)</td>
<td>31 (31.0)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (14.8)</td>
<td>7 (9.9)</td>
<td>10 (10.6)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>100.1 ± 8.3</td>
<td>98.5 ± 7.9</td>
<td>101.2 ± 8.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>15.7 ± 2.7</td>
<td>14.8 ± 2.4</td>
<td>16.2 ± 3.1</td>
</tr>
<tr>
<td>Height for age (Z-score)¹</td>
<td>-0.74 (-1.34, 0.11)</td>
<td>0.28 (-0.4, 1.02)</td>
<td>-0.89 (-1.64, -0.07)</td>
</tr>
<tr>
<td>Weight for age (Z-score)¹</td>
<td>-0.84 (-1.52, -0.26)</td>
<td>0.54 (-0.37, 1.17)</td>
<td>-0.64 (-1.33, 0.02)</td>
</tr>
<tr>
<td>Weight for height (Z-score)¹</td>
<td>-0.67 (-1.1, 0.14)</td>
<td>0.49 (-0.15, 0.99)</td>
<td>-0.11 (-0.63, 0.51)</td>
</tr>
<tr>
<td>Serum vitamin A status (μmol/L)¹</td>
<td>1.35 (1.14, 1.57)</td>
<td>1.18 (1.01, 1.39)</td>
<td>1.06 (0.89, 1.32)</td>
</tr>
<tr>
<td>Hemoglobin concentration (g/L)¹</td>
<td>117 (109.0, 124.1)</td>
<td>114 (109.2, 119.7)</td>
<td>115 (109.5, 122.7)</td>
</tr>
<tr>
<td>Serum ferritin concentration (μg/L)¹</td>
<td>16.1 (12.23, 4.4)</td>
<td>20.7 (16.32, 9.2)</td>
<td>25.3 (17.3, 37.1)</td>
</tr>
</tbody>
</table>

¹ Data are expressed as mean ± SD, number of subjects (percentage), or median (25th, 75th percentiles).
² No significant difference among intervention groups.

Morbidity

Morbidity data were collected for a median of 182 d (interquartile range 180–184 d) for the three intervention groups. Incidence rates and rate ratios for respiratory- and diarrhea-related illnesses and their symptoms are presented in Table 3. There was evidence of a lower incidence rate of respiratory-related illnesses and fewer symptoms of runny nose, cough, and fever for children in group III compared with children in groups I and II, but not for sore throat, skin rash, and other respiratory-related symptoms, such as headache and constipation. Furthermore, despite the undistinguished incidence rate of vomiting, nausea, and stomach pain, the rate of diarrhea-related illness was significantly lower for children in group III than for those in groups I and II. The rate ratios were of similar magnitude to those observed for respiratory-related and diarrhea-related illnesses and symptoms.

Although there was evidence to suggest a decrease in the incidence rate of some magnitude of infectious diseases, there was no significantly or clinically important difference between children in groups I and II.

Moreover, the present data indicated that the duration of respiratory-related illnesses and cough in children in group III was the shortest among the three intervention groups, but symptom duration of runny nose showed no marked difference among groups (Table 4).

No significant difference of morbidity duration was found between groups I and II.

Discussion

Ethical consideration precluded the use of an unsupplemented placebo group; therefore, we used a mutual-controlled strategy that enabled effective comparison of the vitamin A, vitamin A plus iron, and multiple-micronutrient supplement schedule on the infectious morbidity of preschool children.

In this study, compared with vitamin A and vitamin A plus iron, vitamin A combined with other micronutrients significantly decreased diarrhea and respiratory disease morbidities in preschool children 2 to 6 y old in a suburb of Chongqing, China.

Defense against infectious disease is a matter of the highest importance for the health and development of tropical populations. Since the observation that mortality in children is higher in children with vitamin A deficiency [24,25], there has been great interest in determining whether micronutrients interact with immune responses and other aspects of host defense. Although there was no placebo group in this study, it is possible that vitamin A alone was sufficient to decrease diarrhea and respiratory morbidities [26–29].

In developing countries, vitamin A supplementation is currently recommended by the WHO to decrease the burden of childhood morbidities, but the role of vitamin A and multiple micronutrients in preventing infectious illness is less certain.

Although there has been hope that supplementation with multiple micronutrients might be more beneficial that supplementation with a single micronutrient, especially because deficiencies in one micronutrient may limit the functional activity of other micronutrients [30], very few micronutrient fortification trials in preschool children have examined the morbidity of infectious disease. A recent South African trial was unable to detect a morbidity decrease in children supplemented with multiple micronutrients for 6 mo [31]. A similar result was observed in Indonesian infants, where multiple micronutrient supplements improved micronutrient status and anemia but not growth and morbidity [32]. Lopez de Romana G et al. [33] also documented that none of the multiple micronutrient supplements tested prevented growth faltering or the morbidities

Table 2
Measurement outcomes of compliance of the three intervention groups during the trial

<table>
<thead>
<tr>
<th>Supplement doses</th>
<th>Group I (n = 61)</th>
<th>Group II (n = 71)</th>
<th>Group III (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40²</td>
<td>3 (4.9)</td>
<td>0 (0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>40–80³</td>
<td>2 (3.3)</td>
<td>2 (2.8)</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>80–120³</td>
<td>2 (3.3)</td>
<td>3 (4.2)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>120³</td>
<td>54 (88.5)</td>
<td>66 (93.0)</td>
<td>87 (92.4)</td>
</tr>
<tr>
<td>Mean number</td>
<td>112.5</td>
<td>117.5</td>
<td>116.0</td>
</tr>
</tbody>
</table>

² Values are numbers of subjects (percentages).
³ No significant difference among intervention groups.
Table 3  
Incidence of morbidity episodes at follow-up with estimates of the intervention effect

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Incidence/100 child days</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbidity events</td>
<td>I (n = 61)</td>
<td>II (n = 71)</td>
<td>III (n = 94)</td>
</tr>
<tr>
<td>Respiratory related</td>
<td>Morbidity events</td>
<td>Morbidity events</td>
<td>Morbidity events</td>
</tr>
<tr>
<td>Runny nose</td>
<td>202 1.82</td>
<td>241 1.87</td>
<td>245 1.43</td>
</tr>
<tr>
<td>Cough</td>
<td>143 1.29</td>
<td>172 1.32</td>
<td>177 1.03</td>
</tr>
<tr>
<td>Sore throat</td>
<td>21 0.19</td>
<td>26 0.20</td>
<td>37 0.22</td>
</tr>
<tr>
<td>Fever</td>
<td>34 0.31</td>
<td>41 0.32</td>
<td>25 0.15</td>
</tr>
<tr>
<td>Skin rash</td>
<td>8 0.02</td>
<td>6 0.05</td>
<td>6 0.04</td>
</tr>
<tr>
<td>Other</td>
<td>19 0.17</td>
<td>24 0.19</td>
<td>34 0.20</td>
</tr>
<tr>
<td>Diarrhea related</td>
<td>51 0.46</td>
<td>51 0.42</td>
<td>43 0.25</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42 0.38</td>
<td>46 0.35</td>
<td>33 0.19</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 0.05</td>
<td>8 0.06</td>
<td>11 0.06</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 0.12</td>
<td>14 0.11</td>
<td>23 0.13</td>
</tr>
<tr>
<td>Stomach pain</td>
<td>39 0.35</td>
<td>41 0.32</td>
<td>62 0.36</td>
</tr>
</tbody>
</table>

CI, confidence interval

A total of 11 102 child days of follow-up.
A total of 12 922 child days of follow-up.
A total of 17 108 child days of follow-up.
Rate ratio estimated from a negative binomial regression model adjusted for the design strata: age (months), sex, and school.
Table 4
Estimates of follow-up intervention effect for average duration of morbidity in days

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups*</th>
<th>Estimated ratio of geometric means (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group II</td>
</tr>
<tr>
<td>Respiratory related‡</td>
<td>3.1 (27)</td>
<td>2.9 (33)</td>
</tr>
<tr>
<td>Runny nose</td>
<td>3.0 (23)</td>
<td>2.9 (30)</td>
</tr>
<tr>
<td>Cough</td>
<td>2.3 (22)</td>
<td>2.7 (25)</td>
</tr>
</tbody>
</table>

CI, confidence interval
* All values are geometric means (numbers of subjects).
† Estimate of intervention effect adjusted for design strata: age (months), children’s height, weight, sex, nursery, and other socioeconomic status variables listed in Table 1.
‡ Includes at least runny nose, cough, or sore throat.

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References


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