Original Article

# A Randomized Controlled Trial of Zinc Supplementation as Adjuvant Therapy for Dengue Viral Infection in Thai Children

**Sanguansak Rerksuppaphol, Lakkana Rerksuppaphol[1]**

*Department of Pediatrics, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand, [1]Department of Preventive Medicine, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand*

## Abstract

**Background:** Zinc deficiency is common in developing countries and increases the risk for several infectious diseases. Low serum zinc levels have been reported in children with dengue virus infection (DVI). This study aimed to assess the effects of zinc supplementation on DVI outcomes. **Methods:** A double-blinded, randomized trial was conducted in 50 children with dengue fever (DF)/dengue hemorrhagic fever admitted to the pediatric unit of MSMC Srinakharinwirot University Hospital, Thailand, between January 2016 and April 2017. Bis-glycinate zinc or placebo was orally administered three times a day for 5 days or until defervescence. The primary outcome was to evaluate the DVI defervescence phase; the secondary outcome was to assess hospitalization length and presence of severe DVI and zinc deficiency. **Results:** The mean time of defervescence was 29.2 ± 24.0 h in the supplementation group and 38.1 ± 31.5 h in the placebo group ($P$ = 0.270). Meantime of hospital staying was 62.5 ± 23.8 h in the supplementation group and 84.7 ± 34.0 h in placebo group with the mean difference of hospital staying between groups of 22.2 h (95% confidence interval [CI]: 5.5–38.5 h; $P$ = 0.010). Overall prevalence of zinc deficiency was 46%. Serum zinc levels increased from baseline to the end of the study. the mean gain was 26.4 μg/dL (95% CI: 13.6–39.1 μg/dL) in the supplementation group and 14.4 μg/dL (95% CI: 7.4–21.3 μg/dL) in placebo group. No signs of severe DVI were observed in both groups. Zinc supplementation was well tolerated. **Conclusions:** Overcoming zinc deficiency among Thai children may reduce DF duration and limit the hospitalization, in addition to other advantages that normal serum zinc levels have on overall children health.

**Keywords:** *Child, dengue, micronutrients, randomized controlled trial, zinc*

## Introduction

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. Worldwide, its incidence is increased 30 folds over the last 50 years, and approximately 50 million of people are annually infected by dengue virus.[1] Dengue virus infection (DVI) is epidemic in South East Asia countries – Indonesia, Myanmar, Sri Lanka, Thailand, and Timor-Leste-, where more than 70% of the population is at risk.[1] In the tropical monsoon and equatorial zones, *Aedes aegypti* is widespread in both urban and rural areas, multiple virus serotypes are circulating, and dengue is a leading cause of hospitalization and death in children.[1]

In Thailand, between 2000 and 2011, more than 860,000 cases of dengue disease were reported, with an average incidence of 115 cases per 100,000 persons. The mortality was highest during the large 2001 epidemic, while an average of 0.16/100,000 persons was calculated over the entire period of analysis. Between 2003 and 2011, the average case fatality rate reported for the dengue hemorrhagic fever (DHF) was 0.05% (range: 0.03–0.09) and for dengue shock syndrome (DSS) 4.45% (range: 4.04–5.92).[2] Disease incidences remained highest in children aged ≤15 years, with the highest mortality among young children.[2]

DVI may cause mild dengue fever (DF) with an onset of fever accompanied by severe headache, retro-orbital pain, myalgia, arthralgia, abdominal pain, rash, and minor hemorrhage in the form of petechial, epistaxis, or gingival bleeding.[3] Severe DHF/DSS, generally, occurs in those patients who are secondarily infected with a different dengue virus serotype; however, DHF/DSS may occur even in primary infection.[4] The complicated



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***Address for correspondence:***
*Dr. Sanguansak Rerksuppaphol, Department of Pediatrics, Faculty of Medicine, Srinakhariwirot University, 62 Mo 7, Rangsit-Nakorn Nayok Road, Nakornnayok 26120, Thailand.*
*E-mail: sanguansak_r@hotmail.com*

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pathogenesis of DHF/DSS is not fully elucidated: viral and immunological factors play significant roles in major manifestations of DHF/DSS and may partially explain the difference in outcomes. Indeed, viral genetic and structural differences might contribute to virus variation and influence human disease severity[5] and the presence of preexisting heterologous antibodies, which fail to neutralize the current infecting serotype (antibody-dependent enhancement), is a major risk factor for developing DHF/DSS in both infants and adults.[6]

Zinc is a component of more than 300 enzymes involved in catalysis, redox regulation, signaling, and development of neurons;[7] bioinformatics estimates report that 10% of the human proteome contains zinc-binding motives.[8] Zinc is essential for the immune system, and its deficiency has dramatic implications for immune function; therefore, it is not surprising that zinc deficiency increases the risk for several infectious diseases, including diarrhea, pneumonia, and malaria, and that zinc supplementation may provide benefits during the infection.[7,9]

The International Zinc Nutrition Consultative Group has defined a country as at high risk of zinc deficiency when more than 20% of under-five children are stunted, and there is an estimated prevalence of inadequate zinc intake of 25%.[10] Zinc deficiency is common in developing countries, including Thailand where the estimated risk for zinc deficiency is more than 40%.[11] In children with DF, during the toxic phase, serum zinc levels tended to decrease especially in children with diarrhea, dual bacterial infection, and DSS, hepatic encephalopathy.[12] However, a clinically relevant threshold and a relationship between zinc levels and DVI severity are still controversial.[13,14] Data on benefits of zinc supplementation as adjuvant therapy for DVI are lacking; this pilot, double-blinded, randomized, placebo-controlled trial was aimed to assess the effect of zinc supplementation on the outcomes of DVI children.

## Methods

### Study design and population

A randomized, double-blind, placebo-controlled trial was conducted between January 2016 and April 2017 in children admitted to the pediatric unit of MSMC Srinakharinwirot University Hospital with a diagnosis of DF by the modified World Health Organization classification.[1] Patients with signs of hemorrhagic manifestations were classified as DHF, while those who presented circular failure (rapid, weak pulse with narrowing of the pulse pressure ≤20 mmHg) were classified as DSS. Children with acute febrile illness were included in the study in the presence of two or more of the following conditions: (1) nausea and vomiting; (2) rash; (3) aches and pain; (4) tourniquet test positive; (5) leukopenia (white blood cell count ≤5000/mm$^3$); (6) positive for any Dengue serology tests (Dengue IgG/IgM/nonstructural protein 1 [NS1] antigen); and (7) presence of any warning signs (abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, liver enlargement >2 cm, and increased hematocrit concomitant to a rapid decrease in platelet count). Children younger than 1 year, those who regularly assumed vitamins or minerals, or with chronic systemic diseases were excluded from the study.

The study protocol was approved by the Human Ethics Committee of the Srinakharinwirot University. Informed written consent was obtained from parents or legal guardians before enrollment. Parents and children could withdraw from the study at any time. This study is registered with the Thai Clinical Trials Registry (TCTR20151110001).

### Intervention

After enrollment, participants were randomly assigned in 1:1 ratio to receive zinc supplementation or placebo. Randomization was done using a computerized program (GraphPad QuickCals, La Jolla, CA, USA) in a block size of two by a statistician who was not involved in the study. Participants, investigators, and attending clinicians were blinded to code assignment. The code of randomization sequence was opened when the study was completed.

Bis-glycinate zinc (15 mg elemental zinc) was prepared in powder form in single-dose sachets (Qualimed, Bangkok, Thailand) and dissolved in water, before consumption. Zinc was orally administered three times a day for 5 days or until convalescence of fever. The placebo was an oral rehydration solution with identical flavor and packaging (Qualimed, Bangkok, Thailand). Neither zinc nor placebo nor any materials used in the study was donated. There were no influences or any roles from pharmaceutical company or funding agency in the design or conduct of the study the collection, management, or interpretation of the data or involved in any process of the publication. The study was funded solely by Srinakharinwirot University. Treatment of dengue infection, observation, and discharge decision about the patients was done by their attending physicians who were not involved in the implementation phase of the study.

### Data collecting and monitoring

Baseline demographic characteristics and anthropometric data, including sex, age, body weight, and height were recorded. Body mass index was calculated as weight in kilograms/squared height in meters. A detailed of medical history and clinical assessments including the tourniquet test were undertaken by attending physicians. Physical examinations were assessed on the 1$^{st}$ day of hospitalization and every 24 h until discharge by the same physician. Body temperature, pulse rate, blood pressure, and respiratory rate were measured every 4 h by nurses. Blood samples were taken by venepuncture at the admission; a complete blood count and the dengue serology tests were

performed, and serum albumin, aspartate transaminase, alanine transaminase, and serum zinc levels were measured. Dengue-specific IgG/IgM-class antibodies were quantified by an enzyme-linked immunosorbent assay, and dengue NS1 was tested by a lateral flow chromatographic immunoassay using Dengue Combo Test kit (Encode®, Zhuhai, P. R. China). Serum zinc levels were measured by flame atomic absorption spectrometry at baseline and 72 h after supplementation or at the discharge. The time of blood drawing and fasting status were also recorded. Zinc deficiency was defined as serum zinc level lower than thresholds, according to age, sex, fasting status, and time of blood collection. Briefly, the lower cutoff thresholds were as follows: (1) age <10 years: morning 65 μg/dL and afternoon 57 μg/dL; (2) male, age ≥10 years: morning fasting 70 μg/dL, morning nonfasting 66 μg/dL, and afternoon 59 μg/dL; and (3) females, age ≥10 years: morning fasting 74 μg/dL, morning nonfasting 70 μg/dL, and afternoon 61 μg/dL.[15]

Fever was defined as a body temperature of 37.8°C or above; defervescence of fever was defined as the first time that body temperature falling to normal level (37.8°C or below) for two consecutive measurements of 4 h interval. Patients were interviewed with nonleading questions regarding their symptoms and adverse events. Compliance to treatment was as the sum of assumed drug.

The primary outcome was to assess the defervescence phase by assess defervescence time of dengue infection. The secondary outcome was to estimate the duration of hospitalization, the presence of severe DVI, and prevalence of zinc deficiency.

Based on the assumption that the defervescence of fever within 48 h after hospitalization would be expected in 75% of treatment group and 30% of the placebo group, we estimated that a sample size of 22 patients in each group would be required to show a 45% difference between groups, with a power of 80% and a significance level of 0.05. Considering 10% as a dropout, we planned to enroll 50 patients (25 in each group).

### Statistical analysis

A one-sample Kolmogorov–Smirnov test was used to assess whether the variables were normally distributed. Normally distributed variables were described as means and standard deviations; nonnormally distributed variables were presented as medians and interquartile ranges. The Pearson's Chi-square or Fisher's exact test was used to compare proportions between groups, as appropriate. The Student's *t*-test and Mann–Whitney U-test were used to verify the differences of normally distributed and nonnormally distributed variables, respectively. The change in serum zinc levels from baseline was assessed by a paired *t*-test and presented as mean and 95% confidence interval (CI). $P < 0.05$ was considered as statistically significant. Data were analyzed using SPSS version 23.0 statistical package (SPSS, Chicago, IL, USA).

## Results

A total of 53 children with DF or DHF were approached for participation. Of them, 50 accepted were randomly assigned to receive zinc supplementation or placebo [Figure 1]. About 15 (30%) children had DHF, 35 (70%) had DF,

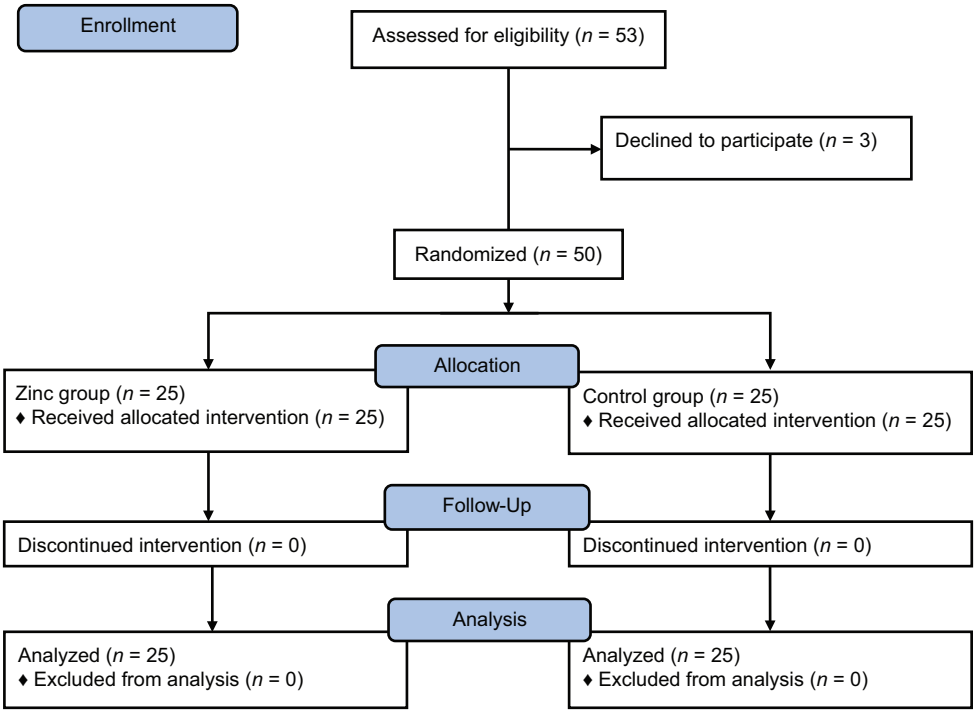


**Figure 1: Study flowchart and enrolment**

none had DSS. A total of 31 (62%) participants were males; the mean age was 6.3 years (range: 1.1–13.8 years). Demographic characteristics, clinical features, and laboratory findings at the hospital admission are detailed in Table 1.

Baseline level of serum zinc in the treatment group was 65.0 ± 14.0 μg/dL compared with 70.8 ± 26.9 μg/dL in placebo group ($P$ = 0.344) [Table 2]. The overall prevalence of zinc deficiency in this population was 46% (48% in treatment group and 44% in placebo, $P$ = 1.000). Baseline serum zinc level in children with DF was 67.5 ± 23.0 μg/dL compared to 68.9 ± 17.8 μg/dL in children with DHF ($P$ = 0.837).

Meantime of defervescence in the treatment group was 29.2 ± 24.0 h versus 38.1 ± 31.5 h in placebo group ($P$ = 0.270). At 48 h after hospitalization, 18 (72%) children in treatment group and 15 (60%) in the placebo group had defervescence ($P$ = 0.551). In the treatment group, the time to defervescence was similar between patients with normal zinc and those with zinc deficiency at the baseline; in the placebo group, patients with normal baseline zinc levels had significantly shorter time to defervescence than patients with zinc deficiency at the baseline (median 24.0 and 48.0 h, respectively; $P$ = 0.029) [Table 2].

Meantime of hospital staying was 62.5 ± 23.8 h in the supplementation group and 84.7 ± 34.0 h in placebo group with the mean difference of hospital staying between groups of 22.2 h (95% CI: 5.5–38.5 h; $P$ = 0.010). Furthermore, in both groups, children with normal zinc levels at the baseline had significantly shorter hospital staying than those with zinc deficiency ($P < 0.05$). At the end of the study, mean serum zinc level in the treatment group was 91.4 ± 28.9 μg/dL compared to 85.2 ± 24.4 μg/dL in placebo group ($P$ = 0.463). The mean gain of serum zinc level from their baseline was 26.4 μg/dL (95% CI: 13.6–39.1 μg/dL) in the treatment group and 14.4 μg/dL (95% CI: 7.4–21.3 μg/dL) in placebo.

No major adverse events were observed during the study. Two children in each group reported mild nausea, and one child in the treatment group reported mild loose stool; all events were resolved without specific treatment. No signs of severe hemorrhage and plasma leakage such as pleural effusion, ascites, or hypovolemic shock were observed. Compliance was good and similar between groups. all children assumed the assigned medication, as per schedule.

**Table 1: Demographic characteristics, clinical features, and laboratory findings of participants**

| | Treatment ($n$=25) | Placebo ($n$=25) | $P$ |
|---|---|---|---|
| Boy, *n* (%) | 14 (56.0) | 17 (68.0) | 0.561 |
| Age (year)[b] | 6.6 (3.6) | 5.9 (3.1) | 0.458 |
| Weight (kg)[b] | 24.0 (12.1) | 23.0 (14.3) | 0.778 |
| Height (cm)[b] | 118.9 (22.4) | 114.3 (18.1) | 0.432 |
| BMI (kg/m$^2$)[b] | 16.07 (3.94) | 16.30 (4.29) | 0.845 |
| Clinical features, *n* (%) | | | |
| Body temperature (°C)[b] | 38.5 (0.8) | 38.4 (0.6) | 0.715 |
| Fever duration before admission (days)[b] | 2.8 (1.6) | 2.9 (1.5) | 0.916 |
| Nausea or vomiting | 22 (88.0) | 22 (88.0) | 1.000 |
| Abdominal pain | 14 (68.0) | 17 (56.0) | 0.561 |
| Headache | 16 (64.0) | 15 (60.0) | 1.000 |
| Myalgia/arthralgia | 7 (28.0) | 5 (20.0) | 0.742 |
| Hepatomegaly | 4 (16.0) | 5 (20.0) | 1.000 |
| Positive tourniquet test | 3 (12.0) | 6 (24.0) | 0.463 |
| Petechial hemorrhage | 2 (8.0) | 3 (12.0) | 1.000 |
| Epistaxis | 1 (4.0) | 1 (4.0) | 1.000 |
| Gastrointestinal bleeding | 1 (4.0) | 2 (8.0) | 1.000 |
| Dengue classification, *n* (%) | | | |
| Dengue fever | 19 (76.0) | 16 (64.0) | 0.538 |
| Dengue hemorrhagic fever | 6 (24.0) | 9 (36.0) | |
| Laboratory findings[b] | | | |
| Hemoglobin (g/dL) | 12.5 (1.5) | 12.4 (1.1) | 0.840 |
| Hematocrit | 37.4 (4.5) | 37.4 (3.2) | 0.966 |
| Leucocyte count (×10$^3$/mm$^3$) | 6.7 (3.4) | 8.2 (3.8) | 0.158 |
| Lymphocytes | 47.8 (7.6) | 45.8 (6.5) | 0.322 |
| Platelets (×10$^3$/mm$^3$) | 96.1 (31.9) | 107.2 (27.8) | 0.196 |
| Albumin (g/dL) | 4.1 (0.4) | 4.0 (0.3) | 0.306 |
| Aspartate transaminase (U/L) | 37.7 (32.8)[a] | 34.7 (17.5) | 0.691 |
| Alanine transaminase (U/L) | 19.0 (11.7)[a] | 27.6 (41.6) | 0.331 |

[a]$n$=24. [b]Presented as mean (SD). SD=Standard deviation, BMI=Body mass index

## Discussion

The present study demonstrated that zinc supplementation (15 mg, three times a day) from the admission significantly shorten the hospital staying in Thai children with DF/DHF; the treatment was well tolerated. At the baseline, 46% of children admitted with DF/DHF had a zinc deficiency; these children had a longer hospital staying compared to those with normal zinc levels, regardless to zinc supplementation. The time to defervescence seemed to not be affected by zinc treatment; however, children with basal normal zinc level and with zinc supplementation showed a shorter duration of fever.

Based on our knowledge, this was the first randomized clinical trial on zinc supplementation in children with DF/DHF. Zinc supplementation has been previously investigated in other infectious diseases, prevalently present in developing countries. Numerous trials were conducted in Asian countries that were at high risk of zinc deficiency on children with acute or persistent diarrhea, including dysentery. A recent systematic review indicated that in the presence of zinc deficiency or malnutrition, zinc supplementation shortened the average duration of diarrhea and reduced the number of children whose diarrhea persisted until 7 days; zinc supplementation was clinically

**Table 2: Serum zinc levels and time to defervescence and hospital stay during the study**

| | Treatment (*n*=25) | Placebo (*n*=25) | *P* |
|---|---|---|---|
| Zinc levels (μg/dL), mean±SD | | | |
| Baseline | 65.0±14.0 | 70.8±26.9 | 0.344 |
| End of study | 91.4±28.9 | 85.2±24.4 | 0.463 |
| Mean difference (95% CI) from baseline | 26.4 (13.6-39.1)[a] | 14.4 (7.4-21.3)[a] | 0.096 |
| Zinc deficiency, *n* (%) | | | |
| Baseline | 12 (48.0) | 11 (44.0) | 1.000 |
| End of study | 3 (12.0) | 6 (24.0) | 0.463 |
| Time to defervescence after admission (hours), mean±SD | 29.2±24.0 | 38.1±31.5 | 0.270 |
| In children with baseline zinc deficiency, median (IQR) | 40.0 (7.0-52.0) | 48.0 (18-73.5) | 0.220 |
| In children with baseline normal zinc levels, median (IQR) | 20.0 (10.5-30.0) | 24.0 (6.0-40.0)[b] | 0.833 |
| Length of hospital staying (hours) | 62.5 (23.8) | 84.7 (34.0) | 0.010 |
| In children with baseline zinc deficiency, median (IQR) | 72.0 (52.0-91.5) | 93.0 (78.0-124.0) | 0.048 |
| In children with baseline normal zinc levels, median (IQR) | 49.0 (43.0-64.3)[b] | 72.0 (45.0-82.0)[b] | 0.169 |

[a]Paired *t*-test, Significant differences from baseline within each group ($P<0.001$), [b]Mann–Whitney U-test, Significant differences from patients with baseline zinc deficiency ($P<0.05$). IQR=Interquartile ranges, SD=Standard deviation, CI=Confidence interval

beneficial for children older than 6 months.[16] In children with HIV, zinc supplementation was safe and reduced diarrheal morbidity, without adverse effects on disease progression.[17] In children with pneumonia, a common respiratory infectious disease, zinc deficiency is highly prevalent (76.0%), but zinc supplementation seemed to not affect clinical outcomes.[18] In dengue disease, the role of zinc deficiency in the pathogenesis is still controversial. Yuliana *et al*. reported that zinc levels significantly differed in children with DF, DHF, or DSS although there was no evidence that serum zinc level was a risk factor for the development of severe dengue infection in children.[13] On the contrary, Widago showed that the clinical severity of dengue disease was similar in the low and high zinc groups, while the number of lymphocytes was significantly different.[14] Laoprasopwattana *et al*. showed that during the toxic phase of DVI, most of the patients had a moderate (40–60 μg/dL) or marked (<40 μg/dL) decrease in plasma zinc levels; in particular, children with a dual bacterial infection, hepatic encephalopathy, and acute diarrhea had plasma zinc values <40 μg/dL.[12] Diarrhea is a well-known cause of zinc loss, and therefore, may represent a possible confounding factor in the attempt to establish a relationship between DF and zinc levels.

Zinc is an essential micronutrient for normal development and function of cells mediating nonspecific immunity, such as neutrophils and natural killer cells, and it plays a role even in the acquired immunity. Indeed, the zinc deficiency prevents outgrowth of T lymphocytes, activation, Th1 cytokine production, and B lymphocytes help. Studies in experimental human models showed that CD8+ CD73+ T lymphocytes, required for antigen recognition, proliferation, and cytolysis were decreased in zinc deficiency.[19] In animal models of enteroaggregative *Escherichia coli* induced-diarrhea, zinc deficiency induced a higher weight loss, stool shedding, and mucus production and reduced the infiltration of leukocytes into the ileum, thus suggesting an impaired immune response.[20] Therefore, in infectious disease, potential benefits from zinc supplementation during the acute phase are to sustain and to optimize the immune response; further studies will better elucidate the role of zinc administration in these conditions, and the clinical significance of prophylactic zinc supplementation that is currently controversial.

The study has some limitations. First, the population size was limited and none severe cases with DSS were included in the study. However, as per our knowledge, this pilot study was the first trial prospectively designed to assess the benefit of zinc supplementation in DVI children; our results should be further confirmed in larger population to completely clarify the potential role of zinc supplementation in the therapeutic management of dengue disease. Second, both treatment and discharge depended on attending physicians; even if well-trained, each attending physician may influence the length of the hospital staying, as per his/her personal experience and approach to the patient. To minimize the potential bias due to different criteria of discharge, we chose to assess the defervescence time as primary outcome as we considered it as the most reliable criterion. Finally, zinc in food intake was not assessed during the follow-up. This may explain the increase of zinc levels in the placebo group.

## Conclusions

This double-blinded, randomized clinical trial indicated that zinc supplementation at the admission to hospital for dengue disease may contribute to shorten the hospital staying. Normal serum zinc levels at the baseline and zinc supplementation during the acute phase of the disease improve the clinical outcomes regarding fever duration. These results may suggest that overcoming zinc deficiency among Thai children may reduce DF duration and limit the hospitalization, in addition to other advantages that normal serum zinc levels have on overall children health.

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## Conflicts of interest

There are no conflicts of interest.

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