Hess SY, Abbeddou S, Yakes Jimenez E, Somé JW, Vosti SA, Ouédraogo ZP, Guissou RM, Ouédraogo JB, Brown KH. **Small-quantity lipid-based nutrient supplements, together with malaria and diarrhea treatment, increase growth and reduce the prevalence of stunting in young Burkinabe children: a cluster-randomized trial.** PLoS ONE, 2015, 10(3): e0122242. doi:10.1371/journal.pone.0122242.

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Introduction

Small quantity lipid-based nutrient supplements (SQ-LNS) have been designed to prevent undernutrition, including stunting, wasting and micronutrient deficiencies [1]. A daily 20 g ration of SQ-LNS provides about 110–120 kcal along with protein, essential fatty acids and 22 micronutrients. Studies assessing the impact of SQ-LNS and medium-quantity LNS (MQ-LNS; at ~50 g or ~250-280 kcal per day) to prevent undernutrition and promote growth and development have found inconsistent results.

This issue of NNA summarizes an article published in *PLoS ONE,* which reported on the results of a community-based, partially masked, placebo-controlled, cluster-randomized intervention trial. The study had two primary objectives: 1) to assess the optimal zinc dose in SQ-LNS; and 2) to compare the impact of the intervention package among children in intervention vs. non-intervention communities [2]. Major outcomes included physical growth, diarrhea, malaria, and change in plasma zinc concentration.

Methods

The trial included two levels of randomization to assign communities to intervention cohort (IC) or non-intervention cohort (NIC), and to assign family compounds (i.e. concessions) within the IC to one of four intervention groups. Twenty-five communities were assigned to the IC and 9 communities to the NIC. Within the IC, 9-months old children meeting the inclusion criteria were allocated to one of following interventions up to 18 months of age: 1) SQ-LNS without zinc, and placebo tablet (LNS-Zn0), 2) SQ-LNS with 5 mg zinc, and placebo tablet (LNS-Zn5), 3) SQ-LNS with 10 mg zinc, and placebo tablet (LNS-Zn10), or 4) SQ-LNS without zinc, and 5 mg zinc tablet (LNS-TabZn5). Children were considered eligible if they were 9 months of age, resided permanently in the area, and had written parental consent. Exclusion criteria were: hemoglobin <50 g/L, weight-

for-length <70% of the median of the National Center for Health Statistics/World Health Organization (NCHS/WHO) growth reference, presence of bipedal edema, other severe illness warranting hospital referral, congenital abnormalities potentially interfering with growth, chronic medical conditions requiring frequent medical attention, history of allergy towards peanuts, and concurrent participation in any other clinical trial.

At baseline and at 18 months of age, children's length, weight, mid-upper arm circumference (MUAC) and head circumference (HC) were measured, and a capillary blood sample was collected for analyses of hemoglobin and a rapid diagnostic test for malaria (RDT). Children in the IC were visited weekly for delivery of intervention products and morbidity surveillance. Children in IC received free treatment for diarrhea, malaria and fever, which was provided during weekly home visits, when appropriate. Children in the NIC did not receive SQ-LNS or tablets from 9 to 18 months of age, nor any morbidity surveillance or illness treatment, but received SQ-LNS from 18 to 27 months after completion of the data collection.

Results and Conclusions:

A total of 2435 children were enrolled in the 4 intervention groups and received daily SQ-LNS with different amounts of zinc; 785 children were enrolled in the NIC (total n=3220). Children were 9.4 months of age at enrollment. Anemia prevalence was high at enrollment with 91% of children having had a hemoglobin concentration < 110 g/L. Malaria prevalence was also high at 9 months of age, 61% having had a positive RDT indicating recent or current malaria infection and all children at enrollment received antimalarial treatment. At 18 months, change in hemoglobin was greater in children in IC than NIC (+8 vs -1g/L, $p<0.0001$), with no difference among the 4 intervention groups. Despite the increase in hemoglobin concentration during the intervention, 79.1% of children in the IC were still anemic compared to 91.1% in NIC.

A venous blood sample was collected to assess zinc status in a randomly selected sub-sample of children (n=403). At baseline, 35% of children had low plasma zinc concentration indicating a high risk of zinc deficiency in the study population. However, there was no difference in change in plasma zinc concentration by 18 months of age, neither among the 4 intervention groups nor between children in IC compared with NIC.

At baseline, mean length-for-age z-score (LAZ) was -1.21 ± 1.1, weight-for-age z-score (WAZ) was -1.42 ± 1.14 and weight-for-length z-score (WLZ) was -0.99 ± 1.05 in all children combined. At 18

months, all z-score indices were significantly greater in IC than NIC. But there were no significant differences among the 4 intervention groups. At baseline, 32% of all children in IC and NIC were stunted. At 18 months, the stunting prevalence was significantly lower in IC (29%) compared to NIC (39%; P<0.0001), with no difference among the 4 intervention groups. Similarly, there was a significant reduction in the wasting prevalence; 8.7% of IC children were wasted compared to 13.5% of NIC children (P=0.0003). MUAC and HC were also significantly larger in children in the IC compared to children in the NIC. These results together suggest that the receipt of the intervention package of SQ-LNS along with illness surveillance and treatment had a significant growth impact independent of the zinc content.

Information regarding diarrhea and malaria incidence was only available for children in the IC because morbidity surveillance was not done in the NIC. During the 9 months intervention period in the IC, the mean (95% confidence interval) prevalence of diarrhea in all four groups combined was 3.08% (2.94, 3.22). There was no difference among the 4 intervention groups. The prevalence of malaria over the 9-months period ranged from 1.56% to 1.67% depending on the group, but these did not differ significantly. More than a third of the diarrhea episodes (36% - 41%) and almost all malaria episodes (99%) were treated. Thus, in the context of freely available treatment for diarrhea and malaria, the addition of 5 to 10 mg zinc to SQ-LNS did not have an impact on illness rates. This lack of impact on the diarrhea prevalence is in contrast to meta-analyses of studies where zinc was provided in tablet or syrup form, which consistently found a reduction in diarrhea prevalence and incidence in children receiving daily supplemental zinc [3,4].

Program and Policy Implications:

Providing SQ-LNS daily with or without zinc, along with malaria and diarrhea treatment, significantly increased growth and reduced stunting, wasting and anemia prevalence in young children. At 18 months of age, 25% less children were stunted in the intervention communities compared to the non-intervention communities. These findings suggest that SQ-LNS is a promising strategy to reduce childhood stunting and wasting among children at risk of stunting, when combined with increased access to health care, although the independent effect of SQ-LNS cannot be determined.

At present, the World Health Organization recommend including 5 mg zinc per day to micronutrient powders, another home fortification product [5].The present study of SQ-LNS did not

find a difference in growth and morbidity outcomes among the 4 intervention groups. Thus, the authors were not able to determine the optimal dose of zinc for SQ-LNS and suggest adding at least 5 mg zinc to SQ-LNS.

NNA Editor's Comments*:

An additionally interesting aspect of the present study was that the adherence to the intervention products was assessed using different methods [6]. Reported adherence to SQ-LNS and tablets was collected during weekly home visits at the time of product distribution. At the same time empty and unused packages were collected to determine the disappearance rate. Both of these indicators suggested very high adherence of >97% to SQ-LNS and tablets. Similarly, high adherence was reported by caregivers in a sub-group of IC children when a research team independent from product distribution asked about knowledge, attitudes and practices. In contrast, only 59% of children were observed to be offered SQ-LNS during 12-hr observations during home visits on two occasions, and only 30% of the children received a tablet during the 12-hr home observation. Moreover, the lack of response in plasma zinc concentration in the group receiving 5 mg zinc in dispersible tablets suggests that the adherence to the tablets was lower than reported. The discrepancy in reported adherence compared with observations and biochemical assessments highlights the need for better methods to assess adherence in community-based supplementation trials and that in some settings, caregivers may over report adherence to please the project staff.
*These comments have been added by the editorial team and are not part of the cited publication.

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