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Original Article

Prevalence of Zinc Deficiency and the Effect of Zinc Supplementation on the Prevention of Acute Respiratory Infections

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Abstract

OBJECTIVE: Acute lower respiratory infections are an important cause of morbidity and mortality in developing countries. Recent randomized trials of zinc supplementation for the prevention of acute lower respiratory tract infections have revealed discrepant findings. The main aim of this study was to evaluate the prevalence of zinc deficiency and the effect of zinc supplementation on respiratory infections.

MATERIAL AND METHODS: A single center, prospective open-label interventional single-arm pre-post study of the effect of oral zinc supplementation in zinc deficient children aged 6 months to 5 years was done. A total of 465 healthy children of age 6 months to 5 years were enrolled in the study for estimation of the prevalence of zinc deficiency. Children having zinc deficiency were recruited to study the efficacy and safety of oral administration of 20 mg zinc for two weeks during a 6-month follow-up period.

RESULTS: There were statistically significant differences between the zinc deficient and non-deficient groups according to modified Kuppuswamy categorization of family status and exclusive breast feeding. There was significant difference in the mid arm circumference between the zinc deficient and non-deficient groups ($p<0.001$). There was significant difference ($p<0.001$) in the number of episodes of acute upper respiratory infections (AURI), mean duration of AURI, and acute lower respiratory infections (ALRI) between the two groups. There was no significant difference in the ALRI episodes between the two groups. After zinc supplementation in zinc deficient children, there was significant decrease in the number of episodes and mean duration of AURI ($p<0.001$) and ALRI ($p<0.001$) within six months after supplementation as compared with the preceding six months before supplementation.

CONCLUSION: This study reveals that a short course of zinc supplementation may reduce the burden of AURI/ALRI among the zinc deficient children, but larger studies are needed.

KEYWORDS: Zinc deficiency, acute respiratory infections, zinc supplementation

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INTRODUCTION

Zinc deficiency is estimated to contribute to over half a million deaths per year in infants and children under 5 years of age [1]. In a cross-sectional study conducted in five states in India, it was found that 43.8% of children 6-60 months of age were zinc deficient [2]. The most common causes of zinc deficiency were found to be inadequate dietary intake, low intake of animal products, limited bioavailability from cereals, and repeated diarrheal illnesses leading to intestinal zinc loss [3]. Zinc is crucial for the normal development and functioning of the cells mediating innate immunity, neutrophils, and natural killer cells [4]. Acute lower respiratory infections (ALRIs) are an important cause of mortality in children under the age of 5 years [5]. Children are more susceptible to zinc deficiency because of poor intestinal absorption and low body stores attributed to undernutrition starting *in utero* [1].

Recent randomized trials of zinc supplementation for the prevention of ALRIs have revealed discrepant findings [6-13]. Also, most studies have evaluated the effect of giving oral zinc for prolonged periods (more than three months) [8,11]. Zinc deficiency leads to stunted growth [14]. The current study was aimed to study the prevalence of serum zinc deficiency in children aged 6 months to 5 years and to assess the effectiveness of oral zinc for two weeks in reducing the morbidity due to AURI/ALRIs in these zinc deficient children.

MATERIAL AND METHODS

Study Design

This study was a prospective, pre-post clinical study to generate real world evidence as recommended by the United States Food and Drug Administration (FDA). The study protocol number AIIMS/IEC/2015/0111 was approved by the in-

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stitutional ethics committee of All India Institute of Medical Sciences (AIIMS), Jodhpur, India. The study was conducted in accordance with the international Council for Harmonization-Good Clinical Practice (ICH-GCP) and other applicable regulatory guidelines.

Participants, Eligibility Criteria, and Settings

This study was conducted from October 2016 to March 2018 in the pediatric department of a tertiary care teaching hospital in Western India. We included 465 healthy children, aged 6 months to 5 years, who came to the pediatric outpatient department (OPD) of AIIMS Jodhpur, India and whose parents were willing to give consent for their participation in the study. Exclusion criteria for the prevalence of zinc deficiency were children who had received zinc supplementation in the past 3 months, severe malnutrition, known immuno-deficiency or on steroids therapy, and chronic co- morbidities. Children with any acute illnesses such as fever, diarrhea, respiratory infection, urinary tract infection, measles, mouth ulcer, and dysentery were excluded at the time of blood collection for estimation of serum zinc but were recalled at a later date when asymptomatic.

The details about the study were explained and a written informed consent was obtained from the parents of all children before recruitment. The data on the socio-economic status, educational status of the parents, the size of the family, and religion were recorded. The pre-treatment period was defined as the six months prior to the administration of oral zinc for 14 days in zinc deficient children. During the pre-treatment period, the number and duration of the episodes of acute upper and lower respiratory infections were recorded through a structured questionnaire. The modified Kuppuswamy scale was used to assess the socio-economic status. The anthropometric parameters including weight, length/height and mid arm circumference of all subjects was done at the time of enrollment.

Estimation of Serum Zinc Levels

Under aseptic conditions, the blood sample was collected from each child and serum zinc levels were estimated. Pediatric vacutainer (Becton Dickinson), which was certified as trace element free, was used for sample collection. The centrifugation of the samples was done at 2,500-3,000 rpm for 10-15 min and the serum samples were stored at -80°C until the estimation. The estimation of the serum zinc levels was done by atomic absorption spectrophotometry [15]. Zinc deficiency was defined as the serum zinc concentration of <10.7 µmol/L [16]. For internal quality control, a certified reference, Seronorm (containing known amounts of zinc in the serum) was used for dilution of set of samples.

MAIN POINTS

- Zinc deficiency prevalence was found to be 43.65% in Western Rajasthan part of India.
- Significant increase in number of AURI and increase duration of AURI and ALRI episodes in zinc deficient children as compared to Zinc Non-deficient children.
- Zinc supplementation leads to decrease in number as well as duration of AURI and ALRI episodes in children below 5 years of age.
- Recommendation for zinc supplementation in Zinc deficient children below five year of age for at least 14 days.

Interventions

Children having zinc deficiency were recruited for the study of the effect of oral administration of zinc. They were given 5 ml of zinc syrup (containing 20 mg zinc sulfate) once daily for 14 days. To ensure compliance, the recruited children were called to the Pediatric OPD on day 7 and 14. Those who did not come for the OPD visit were contacted telephonically to ensure compliance. The data about the side effects were also collected.

Outcomes

The primary outcome was to evaluate the prevalence of serum zinc deficiency. The secondary outcomes were the incidence of acute upper and lower respiratory infections per child, duration of acute respiratory infections, and side effects after zinc supplementation.

Acute upper respiratory infection (AURI): AURI was diagnosed *if the child had cough or cold with or without fever,* as defined by WHO [17].

Acute lower respiratory infection (ALRI): ALRI was diagnosed *if the child had symptoms of cough with difficult and/or rapid breathing or chest in drawing* as seen by the treating physician, as defined by WHO [17].

Analysis and Follow-up

Incidence and duration of AURI and ALRI

All caregivers were given a checklist of the symptoms and signs of AURI/ALRI to be filled by the treating physician. The duration of infection was assessed as the number of days child had symptoms/signs of AURI and ALRI.

Follow-up for AURI/ALRIs was started after 15 days of starting zinc supplementation. Each child was followed up every fortnightly (±2 days) for 6 months after the completion of zinc supplementation. The parents/caregivers were asked to inform regarding the respiratory symptoms, if any, immediately on mobile phone and were asked to visit our OPD or emergency for assessment. At each follow-up visit, the parents/caregivers were asked about the history of AURI/ALRI during the previous 15 days and the treating physician's records (checklist) were also checked to ascertain the diagnosis of AURI/ALRI. Recovery from an AURI/ALRI episode was considered when there were no symptoms of AURI/ALRI for 72 hours following the last day of AURI/ALRI [6]. Any episode subsequently was considered to be a new AURI/ALRI episode.

Sample size calculation

On the basis of the study done by Kapil et al. [2], the prevalence of zinc deficiency was taken to be 44%. The clinical significance level of 0.05 and absolute precision of 5% were considered for the estimation of sample size. A total sample size of 379 was calculated for estimation of zinc deficiency.

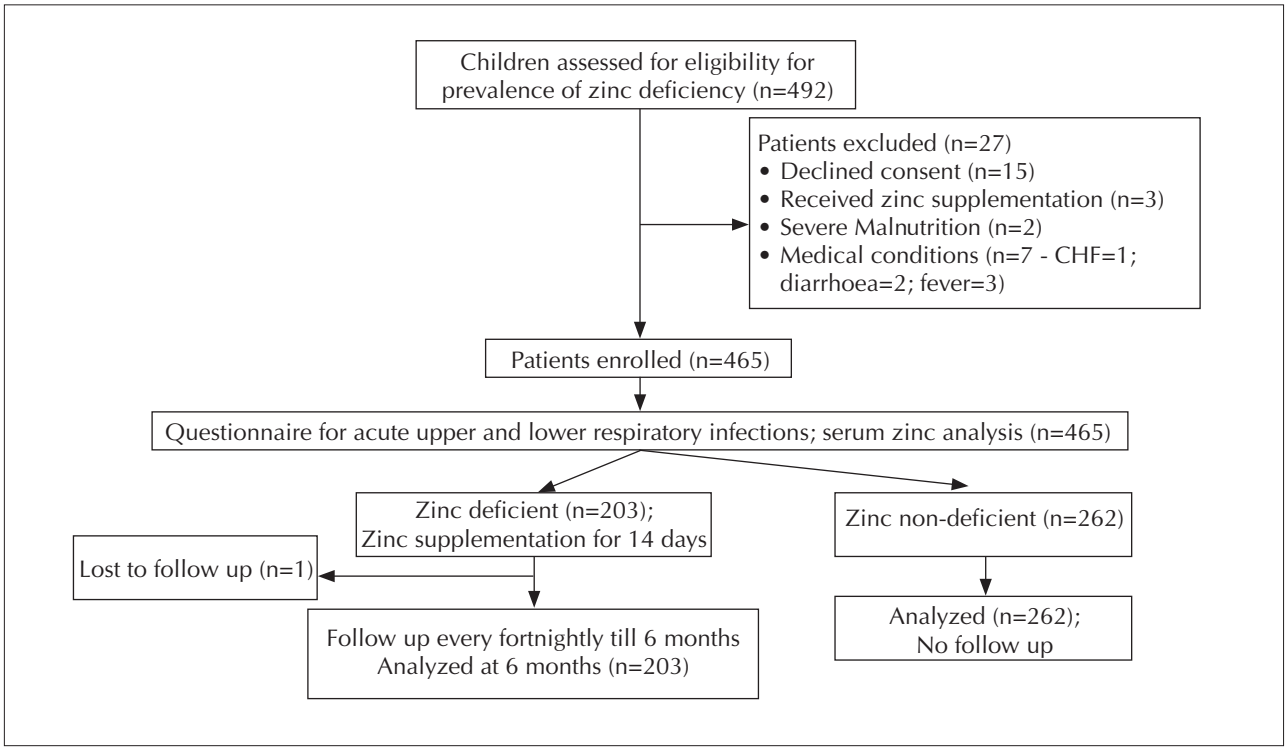

Figure 1. Flow diagram of the participants enrolled in the study

Table 1. Baseline characteristics of zinc deficient and non-deficient children

Baseline characteristics	Zinc deficient (n=203)	Zinc non-deficient (n=262)	p† (2-sided)
Age (months); mean (SD)	28.8 (40.3)	28.4 (37.1)	0.913
Weight (kg); mean (SD)	10.7 (2.90)	10.9 (3.18)	0.436
z-score (SD)	-1.07 (1.18)	-0.91 (1.09)	
Height (cm); mean (SD)	82.6 (12.91)	82.5 (13.06)	0.957
z-score (SD)	-1.23 (1.31)	-1.21 (1.06)	
Modified Kuppuswamy scale; n (%)			
Lower	10 (4.9)	1 (0.4)	<0.001
Lower middle	42 (20.7)	132 (50.4)	
Upper	0 (0)	7 (2.7)	
Upper middle	5 (2.5)	59 (24)	
Upper lower	146 (71.9)	63 (22.5)	
Exclusive breast feeding; n (%)	100 (49.3)	188 (71.8)	<0.001

SD: standard deviation;
†Mean difference between the two groups was analyzed using Student's t-test and categorical data was analyzed by Chi-square or Fisher's Exact test

Statistical Analysis

Numerical data were expressed as mean and standard deviation, whereas categorical data were expressed as percentages or proportions. The incidence was expressed as episodes per child. After testing for normality, normally distributed data were analyzed using the Student's t-test, and Mann-Whitney U test was used for skewed data. Pre-post zinc supplementation incidence and duration of AURI and ALRI were assessed using paired t-test.

Role of Funding source: The funding agency of the study had no role in study design, data collection, analysis, interpretation, or manuscript writing. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

RESULTS

A total of 492 children, aged 6 months to 5 years, were assessed for eligibility, out of which, 465 children were enrolled and evaluated for serum zinc levels. Of the 465, 203 (43.65%) children were found to be zinc deficient (Figure 1). All zinc deficient children were given zinc supplementation for 14 days and were followed up every fortnightly for 6 months. All children were included in the analysis as per intention to treat (ITT) analysis. The ITT analysis was carried out by the last observation carry forward (LOCF) principle.

At baseline, there were no significant differences with regard to mean age, weight, and height whereas there was a significant difference in modified Kuppuswamy categorization ($p<0.001$) of family status between the zinc deficient and non-deficient groups (Table 1). There were significantly greater number of children who were exclusively breast fed in the zinc non-deficient group ($p<0.001$). It was observed that 74.4% of zinc deficient children belonged to the upper class, and 60.4% of them were exclusively breast fed, as compared with 64.3% in lower class family status. There was significant difference in the mid arm circumference between the zinc deficient and non-deficient groups ($p=0.047$). The number of episodes of AURI ($p<0.001$), mean duration of AURI ($p<0.001$), and ALRI ($p<0.001$) were significantly different in the two groups (Table 2). There was no significant difference in the ALRI episodes between the two groups.

Table 2. Anthropometric parameters, incidence of number of episodes of AURI and ALRI, and mean duration of AURI/ALRI in zinc deficient and non-deficient children

Parameters Mean (SD)	Zinc Deficient (n=203)	Zinc Non-Deficient (n=262)	p† (2-sided)
Mid arm circumference (cm); mean (SD)	13.9 (1.24)	14.2 (1.18)	0.047
AURI episodes; mean (SD)	2.0 (0.93)	0.8 (0.73)	<0.001
ALRI episodes; mean (SD)	0.29 (0.46)	0.19 (0.56)	0.059
AURI duration (days) mean (SD)	6.4 (1.79)	4.2 (3.59)	<0.001
ALRI duration (days) mean (SD)	2.3 (3.76)	1.4 (3.15)	<0.001

SD: standard deviation; AURI: acute upper respiratory infection
†-Mean difference between the two groups was analyzed using Student's t-test

Table 3. Incidence of the number of episodes of AURI, ALRI, and mean duration of AURI/ALRI in zinc deficient children before and after zinc supplementation

Parameters mean (SD)	Zinc deficient before treatment (n=203)	Zinc deficient after treatment (n=203)	p† (2-sided)
AURI episodes; mean (SD)	2.0 (0.93)	1.0 (0.75)	<0.001
ALRI episodes; mean (SD)	0.29 (0.46)	0.09 (0.48)	<0.001
AURI duration (days); mean (SD)	6.5 (1.8)	4.3 (2.52)	<0.001
ALRI duration (days); mean (SD)	2.3 (3.77)	0.5 (1.78)	<0.001

SD: standard deviation; AURI: acute upper respiratory infection
†-Mean difference between the two groups was analyzed using paired t-test

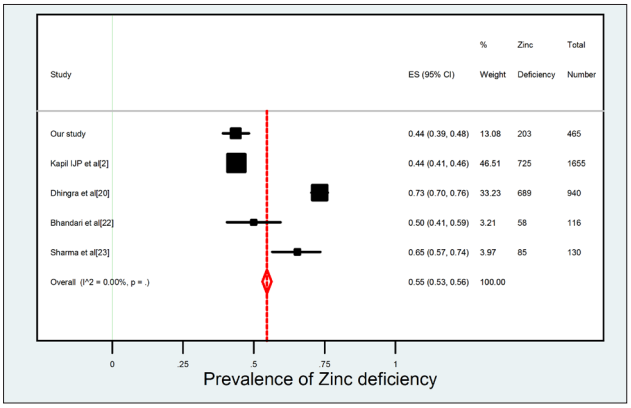

Figure 2. Pooled prevalence of zinc deficiency in children aged 6 months to 6 years

After zinc supplementation in the zinc deficient children, there was significant decrease in the number of episodes of AURI (p<0.001), ALRI (p<0.001), and mean duration of AURI (p<0.001) and ALRI (p<0.001) in six months after the supplementation as compared with that in the preceding six months before supplementation (Table 3). The zinc supplementation resulted in 48% reduction in the AURI episodes [risk ratio (RR): 0.52; 95% confidence interval (CI): 0.44 to 0.61)] and 68% reduction in the ALRI episodes [RR: 0.32; 95% CI: 0.19 to 0.52)].

Out of 203 children who were given the zinc syrup, only 4 children reported vomiting as an adverse drug reaction, which resolved after giving ondansetron syrup. None of the children had any fever, chills, sore throat, and unusual weakness after taking the zinc syrup.

DISCUSSION

Few randomized control trials (RCT) and meta-analyses have shown that zinc supplementation reduces the duration, severity, and incidence of AURI/ALRI [7, 8, 12, 18, 19]. Most of these trials used continuous supplementation and the results have been conflicting. This study aimed to study the prevalence of zinc deficiency in children in western Rajasthan and to examine the effect of zinc given to zinc deficient children, 6 months to 5 years of age, in reducing the incidence of AURI and ALRI.

According to our data, the prevalence of zinc deficiency in children, 6 months to 5 years of age, from western Rajasthan was 43.4%. This prevalence was comparable to the overall prevalence of zinc deficiency (43.8%) in children under five years of age in 5 Indian states, as studied by Kapil et al [2]. According to their study, Odisha had the highest prevalence of zinc deficiency (51.3%), followed by Uttar Pradesh (48.1%), Gujarat (44.2%), Madhya Pradesh (38.9%), and Karnataka (36.2%). Kapil et al. [19] did a cross-sectional study in 260 adolescent school children in the National Capital Territory of Delhi and found the prevalence of zinc deficiency to be 49.4% (50.8% males, 48.2% females). In a community-based study among the preschool children in Delhi, the zinc deficiency was found to be prevalent in 73.3% [20]. A study done by Osei et al. [21] in 499 primary school children in Garhwali Himalayan villages of India found 57.1% of children to be zinc deficient. Bhandari et al reported 50% prevalence of zinc deficiency in children aged 12-59 months and residing in Delhi [22]. According to Sharma et al. [23], the prevalence of zinc deficiency was 65.3% in children aged 4-6 years in Uttar Pradesh. We estimated the pooled prevalence from the studies done in India using STATA. The pooled prevalence in the age group of 6 months to 6 years was found to be 55% [Effect size - 0.55 (95% CI: 0.53 to 0.56)] (Figure 2). Similarly, the overall pooled prevalence in the age group of 6 months to 18 years

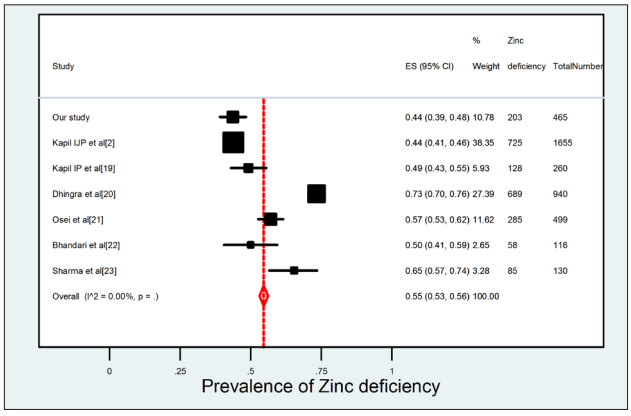

Figure 3. Pooled prevalence of zinc deficiency in children aged 6 months to 18 years

was found to be 55% (effect size-0.55 [95% CI: 0.53 to 0.56]) (Figure 3). The overall pooled prevalence of zinc deficiency was similar in both the age groups, as the two large studies which carry maximum weight for the synthesis of forest plot were included in the analysis of both age groups. In addition, the study done by Osei et al. [21], which carries weight of 12% has prevalence of 57%, close to pooled prevalence of 55%.

We conducted our study from January to December 2017; the pre-treatment period was from January to June and the post-treatment period was from July to December, and both these periods included almost equal number of summer and winter months; therefore, the effect of seasonal features on the frequency of the disease in our study was minimized.

Krebs et al. [1] found correlation between the dietary zinc inadequacy and stunting among children aged under 4 years. Wessels et al. [14] found similar correlation. However, in our study there was no significant difference with regard to mean weight and height but there was significant difference in mid upper arm circumference between the zinc deficient and non-deficient group. The study by Kapil et al. [2] revealed a high prevalence of zinc deficiency in children belonging to Low Socio-economic Index (LSI) in India. Similarly, in our study, there was significant difference in modified Kuppuswamy categorization ($p<0.001$) of family status between the zinc deficient and non-deficient groups.

In our study, zinc supplementation in the zinc deficient children resulted in 48% reduction in the AURI episodes and 68% reduction in the ALRI episodes as compared with the that in the Cochrane review done by Lassi et al. [7], which showed that prophylactic zinc supplementation in children aged 2-59 months resulted in 13% reduction in pneumonia incidence (fixed-effect RR: 0.87; 95% CI: 0.81 to 0.94) and 41% reduction in pneumonia prevalence (random-effect RR: 0.59; 95% CI: 0.35 to 0.99). The subgroup analysis revealed an overall reduction of 21% in pneumonia incidence, as defined by specific clinical criteria after zinc supplementation (i.e., confirmation by chest examination or chest radiograph) (fixed-effect RR: 0.79; 95% CI: 0.71 to 0.88), but no significant reduction in lower specificity pneumonia case definition (i.e. age-specific fast breathing, with or without lower chest indrawing) (fixed-effect RR: 0.95; 95% CI: 0.86 to 1.06). Overall, the Grades of Recommendations, Assessment, Development and Evaluations (GRADE) assessment showed low quality evidence. There was much greater reduction in the incidence of AURI and ALRI in our study as zinc supplementation was administered only to zinc deficient children.

In their meta-analysis of RCTs, Roth et al. [8] found that zinc supplementation in children less than 5 years of age in developing countries reduced the incidence of ALRI, as defined by relatively specific clinical criteria, by 35% [RR: 0.65; 95% CI: 0.52 to 0.82] (assigned each study outcome a score according to the specificity and severity). The authors assumed that in general, specificity and/or severity (i.e. risk of death) were increased by the following elements: diagnosis based on the examination by a trained observer rather than caregiver history; physical signs typically associated with lower rather than upper respiratory tract infection; and signs suggestive of very severe infection and/or hypoxaemia (e.g. lethargy, seizures)) but there was no effect if lower specificity case definitions were applied based on the caregiver report [RR: 1.01; 95% CI: 0.91 to 1.12] or World Health Organization "non-severe pneumonia" [RR: 0.96; 95% CI: 0.86 to 1.08].

A randomized, double-blind, placebo-controlled trial was conducted by Chandyo et al. [9] in which 2 weeks of zinc supplementation was given (10 mg/day for children aged 2-11 months and 20 mg/day for children ≥12 months of age). The zinc levels that were measured 1 and 2.5 months after the end of zinc therapy were not significantly different between the two groups. There was no decrease in the incidence of diarrhea or pneumonia during the next 6 months between the two groups.

Yakoob et al. [10] did a systematic review of all cluster or individual RCTs of zinc supplementation given for more than three months to children aged <5 years in developing countries. The zinc supplementation resulted in 19% and 15% reduction in pneumonia morbidity and mortality, respectively.

Adhikari et al. [11] conducted a double-blind randomized placebo-controlled trial in children 6 months to 5 years of age with a history of recurrent recent respiratory tract infections. The children were randomized to receive 10 mg zinc sulfate or placebo once a day orally for 3 months and were followed up monthly for next 6 months. There was no reduction in the frequency or duration of the respiratory infections overall, but the outcome was better in the children with post-treatment zinc concentrations of >70 mg/dL.

Malik et al. [12] did a double-blind RCT in which they evaluated the incidence and duration of AURI/ALRI in infants aged 6-11 months after prophylactic zinc supplementation for 2 weeks and found a decrease of 12% in the duration of episodes of acute respiratory infections. There was 62% decrease in the incidence of ALRI. However, the overall rate of AURI/ALRI was unaffected.

According to a randomized triple blind community trial done by Sánchez et al [13], the incidence of respiratory infections was significantly lower in the zinc amino acid chelate group as compared with that in the placebo group among the preschool children in child care centers in Colombia.

The strength of this study is that we estimated the prevalence of zinc deficiency in western part of India. Secondly, only zinc deficient children were given oral zinc supplementation for prevention of AURI and ALRI. Additionally, as it was a pre-post study, each child acted as his/her own control, decreasing the variability and hence, increasing the generalizability of the study results to our population. Lastly, the study generates real world evidence as recommended by the United States FDA.

However, there are few limitations of the study. One of the limitations is that it is not a randomized control trial, and thus, the internal validity is decreased. We did not estimate the serum zinc levels after the oral zinc supplementation. A longer follow-up would have increased the strength of evidence generated from the study.

To conclude, zinc deficiency is quite common in Western Rajasthan. Larger cross-sectional studies are needed to estimate the true prevalence of zinc deficiency in children under five years of age. This study is in favor of short course of zinc supplementation in reducing the burden of AURI/ALRI among the zinc deficient children. Future studies are required in this regard to assess the effectiveness of zinc supplementation in reducing the burden of acute respiratory infections in preschool children.

Ethics Committee Approval: Ethics Committee approval for the study protocol number AIIMS/IEC/2015/0111 was obtained from IEC of the All India Institute of Medical Sciences, Jodhpur, India.

Informed Consent: Written informed consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - D.K., S.S., K.S.; Design - D.K., S.S.; Supervision - D.K., S.S., K.S.; Resources - D.K., P.S.; Materials - K.S., P.S., P.P.; Data Collection and/or Processing - D.K., P.P.; Analysis and/or Interpretation - D.K., S.S.; Literature Search - D.K., S.S.; Writing Manuscript - D.K., S.S.; Critical Review - D.K., S.S., K.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

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