DOI: https://doi.org/10.54393/pjhs.v4i04.696

PAKISTAN JOURNAL OF HEALTH SCIENCES
https://thejas.com.pk/index.php/pjhs
Volume 4, Issue 4 (April 2023)

Original Article

A Randomized Controlled Trial on Zinc Supplementation for Prevention of Acute Respiratory Infections in Infants

Arshad Khan[1], Hamayun Anwar[1*], Anila Farhat[2], Ajaz Ahmed[3], Irfan Khan[1] and Irfan Ullah[4]

[1]Department of Pediatric Medicine, Nowshera Medical College/Qazi Hussain Ahmad Medical Complex, Nowshera, Pakistan
[2]Frontier Medical College, Abbottabad, Pakistan
[3]King Abdullah Teaching Hospital, Mansehra, Pakistan
[4]Department of Pediatric Medicine, Nowshera Medical College, Nowshera, Pakistan

ARTICLE INFO

Key Words:
Zinc Supplementation, Acute Respiratory Infections, Infants

How to Cite:
Khan, A. ., Anwar, H. ., Farhat, A. ., Ahmed, A. ., Khan, I. ., & Ullah, I. . (2023). A Randomized Controlled Trial on Zinc Supplementation for Prevention of Acute Respiratory Infections in Infants : Zinc Supplementation for Prevention of ARI. Pakistan Journal of Health Sciences, 4(04). https://doi.org/10.54393/pjhs.v4i04.696

***Corresponding Author:**
Hamayun Anwar
Department of Pediatrics Medicine, Nowshera Medical College/Qazi Hussain Ahmad Medical Complex, Nowshera, Pakistan
hamayun.anwar@yahoo.com

Received Date: 7th April, 2023
Acceptance Date: 28th April, 2023
Published Date: 30th April, 2023

ABSTRACT

There is little evidence that zinc supplementation will be effective in treating acute respiratory infection (ARI), but it may prevent respiratory infections when taken in conjunction with antibiotics. **Objective:** To assess the zinc supplementation for acute respiratory infection prevention in infants. **Methods:** A randomized controlled trail was conducted on 120 acute respiratory infected infants in Pediatric Unit, Qazi Hussain Ahmad Medical Complex, Nowshera from 1st January 2022 to 30th June 2022. Infants having 6-14 months of age with acute respiratory infections were enrolled. Infants were allocated to two groups: Group-I infants receiving Zinc (20 mg/5 mL) in terms of Zinc sulphate (N=60) and Group-II infants taking syrup (Placebo) (N=60). **Results:** Of the total 220 episodes, the frequency of episodes in zinc and placebo group was 106 and 114 respectively, accounting for 7.78 and 8.68 per child year after 5 months. Based on GEE regression model observed an insignificant decrease of 8% (Adjusted IRR 0.89, 95% CI 0.79-1.01) in episodes of acute respiratory infections in zinc group as compared to placebo group. However, acute respiratory infections episodes (Adjusted IRR 0.36, 95% CI: 0.25-0.35) decreased by 60% in zinc group. Zinc supplementation reduced the acute respiratory days significantly by 14% (Adjusted RR 0.83, 95% CI: 0.76-0.92). **Conclusions:** Prophylactic zinc supplementation for two weeks decreased acute lower respiratory tract infection morbidity in apparently healthy infants and improved the infant's recovery from acute respiratory infections and reduced their hospitalization as compared to placebo group.

INTRODUCTION

Zinc is an essential micronutrient in humans that promotes protein synthesis, cell differentiation, and immune system function [1]. Phytates, which limit zinc absorption and utilization, are commonly found in staple foods in many countries such as Thailand and Pakistan [2]. It has been shown that zinc deficiency is associated with pediatric illnesses in multiple randomized controlled trials [3]. Acute respiratory infections (ARIs), particularly acute lower respiratory infections (ALRIs), are among the major causes of children mortality [4-6]. Zinc deficiency is estimated to be responsible for 118,000 fatalities in children under the age of five in underdeveloped nations [7]. Recent studies and meta-analyses have shown that zinc supplementation, both therapeutic and preventative, lowers the length, severity, and frequency of ARIs [8, 9]. In fact, the incidence of stunting in these situations is frequently used to evaluate the amount of zinc deficiency in a community [10]. Zinc influences both non-specific and specific immune activity at several levels. Zinc influences the integrity of the epithelial barrier as well as the activity of neutrophils, natural killer cells, monocytes, and macrophages [11]. As a result, zinc has the potential to be effective in the

DOI: https://doi.org/10.54393/pjhs.v4i04.696

prevention, control, and treatment of infections. The World Health Organization (WHO) and the United Nations Children's Fund advised zinc supplementation for up to two weeks for the treatment of acute diarrhea based on data from many randomized controlled studies and meta-analyses [12]. Similarly, another study investigated the zinc supplementation effect on the frequency and severity of children's respiratory illnesses. The actual countrywide incidence of zinc deficiency in Pakistan is unclear at this time. It is projected that 41.6% of the population is at danger of not getting enough zinc [13]. The high incidence of zinc shortage in poor nations can be ascribed to a zinc malabsorption and lack of zinc-rich foods. Zinc may be found in a variety of meals; however, it is found in higher amounts in fruits, lower concentrations in tubers, vegetable, animal source foods and refined cereals. In contrast, the phytate, a powerful mineral chelator that includes zinc, is commonly present in cereal grains, nuts, and seeds [14]. Despite the fact that zinc deficit is common in Pakistan, no prior research on the zinc supplementation benefits on Pakistani ARI children with have been conducted. The purpose of this study was to investigate the zinc supplementation affected the acute respiratory tract infections treatment in Pakistani infants.

METHODS

A randomized controlled trail was conducted on 120 acute respiratory infected infants in Pediatric Unit, Qazi Hussain Ahmad Medical Complex, Nowshera from 1st January 2022 to 30th June 2022. Infants having 6-14 months of age with acute respiratory infections were enrolled. Infants with a known history of chronic illnesses, such as congenital heart diseases, chronic liver or renal diseases, and immune deficiency or malignancy were excluded. Sample size was estimated based on following criteria: statistical power 80%, α=0.05, type-I errors 0.01, Thus, 104 infants (52 in each group) were required for a 14% decrease in the incidence of ARI (0.05 and power 80%). Taking 5% attrition into account, the final sample size was 120. Consecutive sampling technique was used. Infants were allocated to two groups: Group-I infants receiving Zinc (20 mg/5 mL) in terms of Zinc sulphate (N=60) and Group-II infants taking syrup (Placebo) (N=60). Cessation of ARI (starting period to disappearance of tachypnea, hypoxia, and abnormal pulmonary auscultation) was the primary outcome. Clinical features and hospitalization duration were secondary outcomes. Prior to medication trial, baseline data, detailed medical history, physical examination, and clinical assessment were done and data were recorded. Clinical glass thermometer was used for measuring the axillary temperature. Pulse oximetry was used for measuring the respiratory rate and oxygen saturation till patients were discharged. Patients with axillary temperature ≥37.5°C were defined to have fever. Flame atomic absorption spectrometry was used for the measurement of zinc serum levels at baseline, seven days of supplementation, and before discharge. Data analysis were done in SPSS version 27.0. Mean and standard deviation expressed the quantitative variables whereas categorical parameters were presented as frequencies and percentages. Post-stratification Chi-square test was used for the zinc supplement comparison in both groups. Serum zinc levels from baseline were assessed by paired t-test by taking 95% confidence interval and 5% level of significance.

RESULTS

Of the total 220 episodes, the frequency of episodes in zinc and placebo group was 106 and 114 respectively, accounting for 7.78 and 8.68 per child year after 5 months. Based on GEE regression model observed an insignificant decrease of 8% (Adjusted IRR 0.89, 95% CI 0.79-1.01) in episodes of acute respiratory infections in zinc group as compared to placebo group. However, acute respiratory infections episodes (Adjusted IRR 0.36, 95% CI: 0.25-0.35) decreased by 60% in zinc group. Zinc supplementation reduced the acute respiratory days significantly by 14% (Adjusted RR 0.83, 95% CI: 0.76-0.92). Of the total 120 infants, 78 (65%) were male and 42 (35%) were females. Chest in-drawing, sore throat, and nasal flaring were the prevalent clinical features among acute respiratory infections infants. There was no significant effect of zinc supplementation on the prevalence of acute respiratory infections. Mean concentration of Zinc concentrations on admission in both groups were statistically significant (Group-I 74.8 ± 20.2 mg/dL versus 75.9 ± 21.9 mg/dL in placebo; p=0.835). Serum zinc concentrations at the end of study in Group-I was substantially higher (112.7 ± 28.8 mg/dL) than Group-II (88.3 ± 20.7 mg/dL; p<0.001). Comparing to baseline, mean serum zinc concentration was significantly higher in both groups: mean gain in Group-I and Group-II was 37.8 mg/dL (95% CI: 25.6 to 50.8 mg/dL) and 12.6 mg/dL (95% CI: 3.8 to 21.6 mg/dL) respectively. Table 1 represents the baseline and demographic details of infants.

Table 1: Demographic details of infants

Parameters	Group-I (N=60)	Group-II (N=60)	p-value
Gender N (%)			
Male	46 (76.7)	32 (53.3)	0.346
Females	14 (23.3)	28 (46.7)	
Age (months)			
6-10	21 (35)	26 (43.3)	0.894
11-14	39 (65)	34 (56.7)	
Weight (Kg)	11.3 (4.2)	10.4 (2.3)	0.314
Height (cm)	80.4 (13.6)	79.3 (10.7)	0.492

Infant's clinical features are shown in Table 2.

DOI: https://doi.org/10.54393/pjhs.v4i04.696

Table 2: Clinical features of infants

Characteristics	Group-I (N=60)	Group-II (N=60)	p-value
Temperature (°C)	38.3	38.4	0.572
Respiratory rate (bpm)	50	49	0.262
Pulse (bpm)	164	170	0.217
SBP (mm Hg)	107	106	0.673
DBP (mm Hg)	63	66	0.225
Oxygen saturation %	95.2	94.5	0.836
Rhinorrhea N (%)	58 (96.7)	56 (93.3)	1.000
Sore threat N (%)	54 (90)	54 (90)	0.912
Diarrhea N (%)	8 (13.3)	6 (10)	0.991
Vomiting N (%)	13 (21.7)	17 (28.3)	0.835
Chest in drawing N (%)	57 (95)	58 (96.7)	1.000
Nasal flaring N (%)	53 (88.3)	56 (93.3)	1.000
Hemoglobin g/dL	11.8	11.4	0.372
Hematocrits (%)	35.6	34.8	0.283
Platelet ×103/mm3	384.6	407.2	0.537

Effect of zinc supplementation on the ARI duration and incidence in the study group is shown in Table 3.

Table 3: Effect of zinc supplementation on the ARI duration and incidence in the study group

Outcome	Zinc group	Placebo group	Adjusted IRR
Child year	52.8	49.6	-
Incidence of ARI	7.78	8.68	0.89 (0.79-1.01)
Incidence of AURI	7.1	7.1	0.9 (0.87-1.12)
Days# with ARI	11.2 (6.5)	14.6 (7.9)	0.7 (0.76-0.93)
Days# per episode ARI	3.5 (1.5)	3.7 (1.1)	0.7 (0.77-0.93)

DISCUSSION

The present study mainly focused on the assessment of Zinc supplementation for the prevention of acute respiratory infections in infants and found that compared to placebo, zinc supplementation significantly improved acute respiratory infection recovery and reduced hospitalization duration. Acute respiratory infection's infants were significantly improved in terms of fever, chest-in-drawing, and tachypnea, while restoring normal oxygenation, disappearing wheezes, and normalizing body temperature were improved by zinc intake. Supplementation of zinc bisglycinate, as zinc bisglycinate, was safe and well tolerated. Evidence regarding the zinc supplement possible impact on ARI adjuvant treatment among infants are sparse and contentious, due to the zinc formulas, and assessments of outcome. The current study findings are consistent with other RCT trial's findings according to which zinc supplementation shortened hospital stay and dramatically enhanced recovery from ARI and severe pneumonia [15, 16]. Another study reported that 20 mg/day of zinc acetate supplementation could be beneficial for severe ARI infants. They concluded that zinc supplementation dramatically decreased fever duration and increased recovery rates in critically sick individuals [17]. A previous study by Adhikari *et al.*, found that recovery time from severe ARI increased with zinc supplementation of 20 mg/day or zinc acetate in turn reducing the hospitalization duration. Another research found no statistical significance in zinc supplementation for ARI among infants [18]. Another study reported that zinc sulphate (20 mg/day) failed to demonstrate positive significance of therapy in terms of hospitalization duration. Sánchez *et al.*, found that 20-40 mg/day dose of zinc gluconate supplementation had no significant effect in terms of symptom's recovery and hospitalization duration. In contrast, the risk for ARI readmission increased with zinc supplements [19]. Sharma *et al.*, investigated the prevalence and risk factors of anemia and zinc deficiency among 4–6-year-old children zinc and found that sulphate supplementation (20 mg/day) effectiveness in severe ARI Indian infants [20]. The trial failed to show that adjuvant treatment had substantial clinical benefits or reduced hospitalizations time. Chao *et al.*, [21] conducted their study on Taiwan children and discovered that providing indigenous zinc gluconate supplementation (20-40 mg/day) had no therapeutic benefit for symptom resolution or hospitalizations length. Conversely, ALRI readmission risk was found higher among children who were given zinc supplements. The differences between our findings and those of other writers might be attributable to the varying types and amounts of zinc supplements used. In the current investigation, the zinc dose was roughly suggested daily limit (2-3 times) for the zinc insufficiency treatment. Inorganic zinc is associated with an increased risk of gastrointestinal adverse effects [22]. A previous study by Baqui *et al.*, suggested that organic zinc compound had higher absorption than non-organic [23]. An earlier study by Brown *et al.*, [24] found that organic zinc had lowered bioavailability and is effective and safe procedure employed to infants of zinc bis-glycinate. Zinc's chemical form impacts its bioavailability, and hence the quantity absorbed and assimilated from the intestines after digestion. Zinc can be present as organic complexes in meat and in inorganic salts in plant meals [25-27]. Additionally, the use of amino acid chelates reduces the occurrence of symptoms such as epigastric discomfort, nausea, stomach cramps, and vomiting, and diarrhea [28]. The process by which zinc supplementation alleviates ARI symptoms is uncertain. In theory, zinc is required for cell proliferation and protein synthesis, and it is crucial for respiratory cell integrity [29, 30]. In respiratory infections infants, cellular damage and inflammation at airway might be worsen by zinc deficiency [31]. Based on these findings, contributes to better clinical outcomes, it is reasonable to believe that elevating serum zinc levels during ARI. Thai children with an estimated risk of zinc insufficiency greater than 40% may benefit from zinc supplementation, not only

DOI: https://doi.org/10.54393/pjhs.v4i04.696

to boost dietary micronutrient intake, but also to promote illness recovery.

CONCLUSIONS

Prophylactic zinc supplementation for two weeks decreased acute lower respiratory tract infection morbidity in apparently healthy infants aged 6 to 14 months during follow-up. Also, the present study indicated that zinc supplementation improved the infant's recovery from acute respiratory infections and reduced their hospitalization as compared to placebo group.

Authors Contribution

Conceptualization: AK
Methodology: HA, IU, AK
Formal analysis: AA
Writing-review and editing: AF, IK

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

REFERENCES

[1] Barffour MA, Hinnouho GM, Wessells KR, Kounnavong S, Ratsavong K, Sitthideth D, *et al*. Effects of therapeutic zinc supplementation for diarrhea and two preventive zinc supplementation regimens on the incidence and duration of diarrhea and acute respiratory tract infections in rural Laotian children: A randomized controlled trial. Journal of Global Health. 2020 Jun; 10(1): 010424. doi: 10.7189/jogh.10.010424.

[2] Rerksuppaphol S and Rerksuppaphol L. A randomized controlled trial of zinc supplementation in the treatment of acute respiratory tract infection in Thai children. Pediatric Reports. 2019 May; 11(2) :7954. doi: 10.4081/pr.2019.7954.

[3] Khera D, Singh S, Purohit P, Sharma P, Singh K. Prevalence of Zinc Deficiency and the Effect of Zinc Supplementation on the Prevention of Acute Respiratory Infections. Turkish Thoracic Journal. 2020 Nov; 21(6): 371.

[4] Moshtagh M and Amiri R. Role of zinc supplementation in the improvement of acute respiratory infections among Iranian children: a systematic review. Tanaffos. 2020 Jan; 19(1): 1.

[5] A, Taneja DK, Devasenapathy N, Rajeshwari K. Zinc supplementation for prevention of acute respiratory infections in infants: a randomized controlled trial. Indian Pediatrics. 2014 Oct; 51: 780-4. doi: 10.1007/s13312-014-0503-z.

[6] Wessells KR, Brown KH, Arnold CD, Barffour MA, Hinnouho GM, Killilea DW, *et al*. Plasma and nail zinc concentrations, but not hair zinc, respond positively to two different forms of preventive zinc supplementation in young laotian children: a randomized controlled trial. Biological Trace Element Research. 2021 Feb; 199(2): 442-52. doi: Malik 10.1007/s12011-020-02163-2.

[7] Mokdad AH, Forouzanfar MH, Daoud F, El Bcheraoui C, Moradi-Lakeh M, Khalil I, *et al*. Health in times of uncertainty in the eastern Mediterranean region, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Global Health 2016 Oct; 4(10): e704–13.

[8] Khoushabi F, Shadan MR, Miri A, Sharifi-Rad J. Determination of Maternal Serum Zinc, Iron, Calcium and Magnesium during Pregnancy in Pregnant Women and Umbilical Cord Blood and Their Association with Outcome of Pregnancy. Materia Socio-medica 2016 Apr; 28(2): 104-7. doi: 10.5455/msm.2016.28.104-107.

[9] Neyestani TR, Nikooyeh B, Hajifaraji M, Kalayi A. The prevalence of zinc deficiency and its correlation with iron status and economical living area in 9-12-year-old children. International Journal of Vitamin Nutrition Research. 2016 Feb; 86(1-2): 18-26. doi: 10.1024/0300-9831/a000240.

[10] Rahmati M, Safdarian F, Zakeri M, Zare S. The prevalence of zinc deficiency in 6-month to 12-year-old children in Bandar Abbas in 2013. Electronic Physician. 2017 Aug; 9(8): 5088. doi: 10.19082/5088.

[11] Sampaio DL, De Mattos ÂP, Ribeiro TC, Leite ME, Cole CR, Costa-Ribeiro Jr H. Zinc and other micronutrients supplementation through the use of sprinkles: impact on the occurrence of diarrhea and respiratory infections in institutionalized children. Jornal de Pediatria. 2013 May; 89(3): 286-93. doi: 10.1016/j.jped.2012.11.004.

[12] World Health Organization. UNICEF.: Zinc supplementation in the management of diarrhoea. [Last Cited: 28th September 2016]. Available at: http://wwwwhoint/elena/titles/zinc_diarrhoea/en/2016

[13] Bonaventura P, Benedetti G, Albarède F, Miossec P. Zinc and its role in immunity and inflammation. Autoimmunity Reviews. 2015 Apr; 14(4): 277-85. doi: 10.1016/j.autrev.2014.11.008.

[14] Roohani N, Hurrell R, Kelishadi R, Schulin R. Zinc and its importance for human health: An integrative review. Journal of research in medical sciences: the

DOI: https://doi.org/10.54393/pjhs.v4i04.696

official journal of Isfahan University of Medical Sciences. 2013 Feb; 18(2): 144.

[15] Read SA, Obeid S, Ahlenstiel C, Ahlenstiel G. The role of zinc in antiviral immunity. Advances in nutrition. 2019 Jul; 10(4): 696-710. doi: 10.1093/advances/nmz013

[16] Lassi ZS, Moin A, Bhutta ZA. Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months. Cochrane Database of Syst Rev. 2016;12:CD005978. doi: 10.1002/14651858.CD005978.pub3.

[17] Malik A, Taneja DK, Devasenapathy N, Rajeshwari K. Zinc supplementation for prevention of acute respiratory infections in infants: a randomized controlled trial. Indian Pediatrics. 2014 Oct; 51:780-4. doi: 10.1007/s13312-014-0503-z.

[18] Adhikari DD and Das S. Role of zinc supplementation in the outcome of repeated acute respiratory infections in Indian children: a randomized double blind placebo-controlled clinical trial. Research Journal of Pharmacy and Technology. 2016;9(4):457-8. doi: 10.5958/0974-360X.2016.00084.6.

[19] Sánchez J, Villada OA, Rojas ML, Montoya L, Díaz A, Vargas C, *et al*. Effect of zinc amino acid chelate and zinc sulfate in the incidence of respiratory infection and diarrhea among preschool children in child daycare centers. Biomedica. 2014 Mar; 34(1): 79-91. doi: 10.7705/biomedica.v34i1.1581.

[20] Sharma U and Yadav N. Prevalence and risk factors of anemia and zinc deficiency among 4–6-year-old children of Allahabad district, Uttar Pradesh. Indian Journal of Public Health. 2019 Mar; 63(1) :79–82. doi: 10.4103/ijph.IJPH_342_17.

[21] Chao HC, Chang YJ, Huang WL. Cut-off Serum Zinc Concentration Affecting the Appetite, Growth, and Nutrition Status of Undernourished Children Supplemented with Zinc. Nutrition in Clinical Practice. 2018 Oct; 33(5): 701-10. doi: 10.1002/ncp.10079.

[22] Nair H, Simões EA, Rudan I, Gessner BD, Azziz-Baumgartner E, Zhang JS, *et al*. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. The Lancet. 2013 Apr; 381(9875): 1380-90. doi: 10.1016/S0140-6736(12)61901-1.

[23] Baqui AH, Black RE, El Arifeen S, Yunus M, Chakraborty J, Ahmed S, *et al*. Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. Bmj. 2002 Nov; 325(7372): 1059. doi: 10.1136/bmj.325.7372.1059.

[24] Brown KH, Sonja YS, Peerson JM, Baker SK. Does preventive zinc supplementation of infants and young children affect their risk of selected illnesses, survival, and physical growth. Food Nutrition Bulletin. 2009; 30: S12-S40. doi: 10.1177/15648265090301S103.

[25] Wang L and Song Y. Efficacy of zinc given as an adjunct to the treatment of severe pneumonia: A meta-analysis of randomized, double-blind and placebo-controlled trials. The Clinical Respiratory Journal. 2018 Mar; 12(3): 857-64. doi: 10.1111/crj.12646.

[26] Yuan X, Qian SY, Li Z, Zhang ZZ. Effect of zinc supplementation on infants with severe pneumonia. World Journal of Pediatrics. 2016 May; 12: 166-9. doi: 10.1007/s12519-015-0072-9.

[27] Wessells KR, Brown KH, Kounnavong S, Barffour MA, Hinnouho GM, Sayasone S, *et al*. Comparison of two forms of daily preventive zinc supplementation versus therapeutic zinc supplementation for diarrhea on young children's physical growth and risk of infection: study design and rationale for a randomized controlled trial. BMC Nutrition. 2018 Dec; 4: 1-9. doi: 10.1186/s40795-018-0247-6 .

[28] SoukAloun D, Douangbouphaa V, Phetsouvanh R, Sibounheuang B, Vongsouvat M, Chanmala K, *et al*. Rotavirus diarrhea in hospitalized children under 5 years of age in Vientiane, Lao PDR, 2009–2015. Vaccine. 2018 Dec; 36(51): 7878-82. doi: 10.1016/j.vaccine.2018.04.004.

[29] McDonald CM, Manji KP, Kisenge R, Aboud S, Spiegelman D, Fawzi WW, *et al*. Daily zinc but not multivitamin supplementation reduces diarrhea and upper respiratory infections in Tanzanian infants: a randomized, double-blind, placebo-controlled clinical trial. The Journal of Nutrition. 2015 Sep; 145(9): 2153-60. doi: 10.3945/jn.115.212308.

[30] de Medeiros Rocha ÉD, de Brito NJ, Dantas MM, de Araújo Silva A, das Graças Almeida M, Brandão-Neto J. Effect of zinc supplementation on GH, IGF1, IGFBP3, OCN, and ALP in non-zinc-deficient children. Journal of the American College of Nutrition. 2015 Jul; 34(4): 290-9. doi: 10.1080/07315724.2014.929511.

[31] Cho HE, Myung SK, Cho H. Efficacy of Vitamin D supplements in prevention of acute respiratory infection: A meta-analysis for randomized controlled trials. Nutrients. 2022 Feb; 14(4): 818. doi: 10.3390/nu14040818.