National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

The effect of zinc and Vitamin A supplements in treating and reducing the incidence of upper respiratory tract infections in children

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Received: January 31, 2018; **Accepted:** March 06, 2018

ABSTRACT

Background: Supplementation of zinc and Vitamin A shows inconsistent effects on the respiratory morbidity in children in developing countries. Aims and Objectives: The aim of this study is to evaluate the effect of zinc and zinc + Vitamin A supplementation on the acute upper respiratory infections (AURTIs) in the pediatric patients aged between 2 and 12 years. **Materials and Methods:** A randomized double-blind placebo-controlled trial was employed in the present study. A total of 80 children suffering with AURTI were randomly assigned to one of three intervention groups: Placebo group, daily zinc (2–2.5 mg elemental zinc/Kg divided on 1–3 doses) group, and daily zinc + once dosing of Vitamin A (50000 IU) group in addition to the required treatment for their respiratory illness. Differential blood count analysis and C-reactive protein (C-RP) were assayed on days 1 and 5, and then, zinc or placebo was given daily for 6 months to the children, which were followed up and monitored once weekly for 6 months. The information regarding adverse effects, AURTI incidence, and missing school days were then collected. **Results:** The total white blood cells count, neutrophil (staph) percentage, and C-RP significantly decreased by post-supplementation with both zinc and zinc + Vitamin A. Monocytes percentage showed a significant increase by post-supplementation with zinc + Vitamin A ($P = 0.011$). In addition, AURTI and school absence incidences were significantly decreased in both zinc and zinc + Vitamin A recipients compared to placebo patients. **Conclusion:** We concluded that zinc alone or simultaneous zinc and Vitamin A supplementation in AURTI patients significantly improved the clinical outcome by improving the immune status.

KEY WORDS: Zinc; Vitamin A; Supplements; Upper Respiratory Infections; Children

INTRODUCTION

Respiratory tract infections (RTIs) are common in children and drive the majority of antibiotic prescribing for this population.[1] When parental time off work is added to the costs of health care, RTIs pose a major financial burden.[2]

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2018.8.0104206032018	

Upper RTI (URTI) has shown the largest impact on the disease burden among children.[3] It has been detected as a frequent cause of morbidity in neonates and young children which predisposes to the risks of being affected with many diseases such as otitis media, sinusitis, or asthma attacks.[4] In Egypt, a study showed a high prevalence of acute respiratory infections (ARIs) in schoolchildren (51.23%).[5]

The major global burden of child morbidity and mortality due to acute URTI has focused the attention on the nutrition role in promoting children survival. Malnutrition has been found as a major risk factor for recurrent RTIs.[6] One of the

most essential nutritional issues in middle- and low-income countries is the deficiency of zinc and Vitamin A.

Zinc has known as a vital dietary supplement since long ago. Zinc acts as an antioxidant, microtubule stabilizer, antiapoptotic agent, growth cofactor, anti-inflammatory agent, and even cytoprotective against toxins and inflammatory mediators.[7] Moreover, Vitamin A is required for the proper functioning of a lot of metabolic and physiologic activities. Vision, hematopoiesis, embryonic development, skin cell differentiation, immune system function, and gene transcription all require Vitamin A.[8]

Worldwide, many developed nations' researches have reported zinc and Vitamin A deficiencies as major contributors to child mortality.[9] Zinc deficiency has been attributed to poor nutrition, restricted bioavailability from local diets, and losses during diarrheal illness,[10] while the reasons of Vitamin A deficiency are due to poor dietary intake, early weaning from breast milk, or from malabsorption of lipids and zinc, which is necessary for Vitamin A uptake.[8] Zn is essential for the synthesis of retinol-binding protein (RBP). Zinc deficiency can depress the synthesis of RBP in the liver and lead to lower concentrations of RBP in the plasma, and Vitamin A supplementation alone fails to recover this specific condition.[11,12] Despite many children may have seriously low levels of Vitamin A, still no external signs to be detected, which may lead silently to children potential infections and death.[9]

Zinc and Vitamin A deficiency has dramatic implications on immune functions. As a matter of fact, previous studies have effectively related childhood zinc and Vitamin A deficiency to increase the risk of RTIs, diarrheal disease, and growth failure.[10,13] This has motivated researchers to investigate the potential role of such supplements in preventing such infective illnesses.[13,14] Although this has been previously investigated,[6,15-17] many studies results have been heterogeneous, biased, and inconsistent and warranted further investigation.[17]

Recently, researches have focused on studying the effect of zinc and Vitamin A supplementations on problematic (URTI). Zinc supplementation has been reported to reduce the risk or the effects of URTI such as the common cold or flu.[18-21] However, several other studies have reported conflicting results that zinc was only beneficial for boys[22] or for children with malnutrition.[23] Larger discrepancies have been reported with Vitamin A supplementation studies. It was found that Vitamin A supplementation reduces measles morbidity; however, its effects on diarrhea and non-measles respiratory infection still remain uncertain and need further verification.[24,25]

This study estimates the efficacy of zinc and Vitamin A as adjunct treatment in Egyptian children with acute upper respiratory infections (AURTIs) and their effects on URTI and school absence incidences. We want to prove whether using zinc and Vitamin A will reduce the frequency and severity of childhood respiratory illnesses or not.

MATERIALS AND METHODS

Patients

A randomized, double-blind, placebo-controlled, interventional study was conducted on 80 pediatric patients (33 males and 47 females). Inclusion criteria included children aged between 2 and 12 years old. Patients diagnosed with acute URTI such as a common cold, pharyngitis, tonsillitis, laryngitis, otitis media, sinusitis, or epiglottitis were randomly recruited from outpatient pediatric clinics of Nasser Central Hospital in Naser town, Beni-Suef, Egypt, from September 2014 to February 2015. The Ethics Committee of the Faculty of Medicine Beni-Suef University (FM-BSU/REC), Beni-Suef, Egypt, approved the study protocol. Informed consent was obtained from all guardians of participating children included in the study. Major exclusion criteria were children suffering from congenital diseases, immune deficiency, metabolic diseases, or severe malnutrition (weight for age <60% of the World Health Organization (WHO)/National Center for Health Statistics reference).[26]

Procedure

The eligible patients' baseline demographic and clinical data were recorded. Patients were subjected to a complete and detailed medical history, physical, and clinical examination. Eligible pediatric patients were randomly assigned into one of three interventional treatment groups, as presented in Table 1. Random numbers were utilized to allocate each child to receive either zinc or zinc + Vitamin A or a placebo syrup for the study period.

Zinc or placebo was taken daily for 6 months next to their acute illness standard treatment utilized as per the WHO guidelines.[27] Placebo and zinc syrups and placebo and Vitamin A capsule were made identical in appearance. Investigators made regular visits (once weekly) to study

Table 1: Three interventional treatment groups

Group 1 (*n*=30)	Assigned to receive placebo in addition to the required treatment for their illnesses
Group 2 (*n*=30)	Assigned to receive zinc supplementation (2–2.5 mg elemental zinc/kg divided on 1–3 doses, zinc origin®10 mg/5 ml syrup, Origin International Pharma company Ltd., Egypt), in addition to, the required treatment for their illnesses
Group 3 (*n*=30)	Assigned to receive zinc+single dose Vitamin A supplementation (50000 IU, A Viton®, Kahira Pharm and Chem. Ind. Co, Egypt) in addition to the required treatment for their illnesses

patients for additional monitoring of any new incidence of an URTI such as a common cold, pharyngitis, tonsillitis, laryngitis, otitis media, sinusitis, or epiglottitis. At each visit, mothers were asked about respiratory illness incidence in the previous 7 days. Moreover, school absence days due to illness were also recorded during 6 months' study period.

An acute (URTI) episode was defined as the presence of one or two of the following clinical symptoms experienced for at least 1 day: Runny nose, cough, sore throat, otalgia, muscle ache, and elevated body temperature, without the signs of rapid and difficult breathing. Three symptom-free days were required before defining a new acute (URTI) episode. The number of URTI incidences and missing school days were recorded for each patient and used to monitor patient morbidity.[28,29] Investigators monitored syrups consumption and recorded compliance data. Non-compliance was defined as syrup consumption of <75% of the total supplement days.

Blood Sampling

At enrolment and 4 days later of the study, non-fasting venous blood samples (3 cm^3) were withdrawn from each patient for the determination of complete blood count (CBC) with differential count (2 cm^3) and C-reactive protein (CRP) quantitatively (1 cm^3). CBC with differential count was done automated by Cell Dyn 3700 device followed by manual differential count, while CRP was determined quantitatively with latex mechanism. CRP latex reagent is a suspension of polystyrene particles sensitized with antihuman CRP. The approximate CRP concentration in serum can be calculated by the following formula: CRP mg/L = highest positive dilution × 6 (as the reagent sensitivity is 6 mg/L).

Statistical Methods

SPSS V18.0 (SPSS Inc., Chicago, USA) was used for statistical comparison of all treatment groups using student *t*-test. The calculated *P*-value is considered statistically significant if ≤ 0.05.

RESULTS

The baseline demographic and clinical characteristics of patients were presented in Table 2. A total of 80 randomly selected pediatric patients (33 males and 47 females) were recruited in the study. Patients were randomly assigned into three treatment groups: Group 1 of 20 patients (4 males and 16 females) with mean ± standard deviation (SD) age (year) of 6.2 ± 3.5, Group 2 of 30 patients (12 males and 18 females) with mean ± SD age 6.7 ± 2.8, and Group 3 of 30 patients (17 males and 13 females) with mean ± SD age 7.5 ± 2.6. As presented in Table 2, all study treatment groups were well balanced with respect to baseline demographic and clinical characteristics or with respect to their current medical condition.

Differential CBC Results

Table 3 shows that hemoglobin (Hgb) results were not affected with either zinc or zinc + Vitamin A supplementation. The total white blood cells (WBCs) count decreased significantly (P = 0.001) post-zinc and zinc + Vitamin A treatment. However, neutrophil (staph) percent values significantly decreased following Zn supplementation (P = 0.001) and following zinc + Vitamin A supplementation (P = 0.001). Comparable reductions were observed with zinc and zinc + Vitamin A treatment groups. For lymphocytes percentage values, they significantly increased in control group (P = 0.008), post-zinc treatment (P = 0.001), and post-zinc + Vitamin A treatment (P = 0.018).

In addition, monocytes percentage values did not show any significant difference post-Zn treatment group and changed significantly (P = 0.011) post-Zn + Vitamin A supplements. Regarding CRP values, a highly significant (P = 0.001) decrease for both treatment groups compared to placebo (P = 0.019) was achieved. Non-significant difference was reported between Zinc and Zinc + Vitamin A groups in (CRP) values.

AURTIs Morbidity

Monitoring of URTI and school absence incidences during the study period revealed that the mean ± SD of URTI incidences were 2.9 ± 2.3, 1.7 ± 2.3, and 1.5 ± 1.9 for the placebo, zinc, and zinc + Vitamin A, respectively. Moreover, missing school days per student during the study period were 1.7 ± 1.5, 0.8 ± 0.5, and 0.6 ± 2.2 for the placebo, zinc, and zinc + Vitamin A recipients, respectively.

Adverse Effects

Apart from four participants in the zinc + Vitamin A group who complained from mild gastrointestinal discomfort that resolved quickly, all treatment were well tolerated. None of the patients required hospitalization, stopping the treatment regimen, medical attention, or withdrawal from the trial.

Compliance

During the whole study treatment period, 96.6%, 97.3%, and 95.2% of subjects consumed >95% of their medication in placebo, zinc, and zinc + Vitamin A recipient.

DISCUSSION

Malnutrition is considered as major risk factors for a worldwide increased child morbidity and mortality from infectious diseases. Thus, interventional micronutrient supplementation has been known as one of the most important cost-effective approaches to boost immune function for prevention or treatment of different infections. Understanding the biological mechanism and changes in hematological

Table 2: Baseline demographic and clinical characteristics of the study patients (*n*=80)

Demographic details mean±SD or *n* (%)	Group 1 (*n*=20) standard treatment+placebo	Group 2 (*n*=30) standard treatment+zinc	Group 3 (*n*=30) standard treatment+zinc+Vitamin A
Age (year)	6.2±3.5	6.7±2.8	7.5±2.6
Sex			
Male	4 (20)	12 (40)	17 (56.7)
Female	16 (80)	18 (60)	13 (43.3)
Breastfeeding duration			
Non	-	2 (6.6)	1 (3.3)
6–12	10 (50)	16 (53.3)	14 (46.6)
>12	10 (50)	12 (40)	15 (30)
Socioeconomic standards			
Low	14 (75)	21 (70)	22 (73.3)
Middle	6 (25)	9 (30)	8 (26.6)
Symptoms onset			
1st day	1 (5)	2 (6.7)	
2nd day	7 (35)	9 (30)	8 (26.6)
3rd day	9 (45)	16 (53.3)	17 (56.7)
>3rd day	3 (15)	3 (10)	5 (16.6)
Symptoms			
Fever	10 (50)	19 (63.3)	15 (50)
Running nose	2 (10)	14 (46.6)	21 (70)
Cough	13 (65)	10 (33.3)	6 (20)
Sore throat	17 (85)	29 (96.6)	28 (93.3)
Ear pain	11 (55)	7 (23.3)	2 (6.6)
Vomiting	1 (5)	1 (3.3)	2 (6.6)
Nose secretions			
Watery	7 (35)	10 (3.3)	13 (43.3)
Mucoid	3 (15)	14 (46.6)	18 (60)
Purulent	1 (5)		
Throat			
Congested	17 (85)	25 (83.3)	20 (66.6)
Tonsil follicles		4 (13.3)	8 (26.6)
Cervical lymph node			
Unilateral	2 (100)	3 (10)	4 (13.3)
Bilateral	6 (30)	8 (26.6)	7 (23.3)
Eye redness			
4 (20)	4 (13.3)	-	Eye redness
Provisional diagnosis			
Pharyngitis	12 (60)	18 (60)	13 (43.3)
Tonsillitis	8 (40)	11 (36.3)	16 (53.3)
Otitis media		1 (3.3)	
Common cold			1 (3.3)
URT disease course			
Stable	6 (30)	5 (16.6)	2 (6.6)
Progressive	14 (70)	25 (83.3)	28 (93.3)
Regressive			
Recurrent URTI history/year			
Once	1 (5)		

(Contd...)

Table 2: (*Continued*)

Demographic details mean±SD or *n* (%)	Group 1 (*n*=20) standard treatment+placebo	Group 2 (*n*=30) standard treatment+zinc	Group 3 (*n*=30) standard treatment+zinc+Vitamin A
2			
3	4 (20)	1 (3.3)	4 (13.3)
4	5 (25)	13 (43.3)	9 (30)
>4	10 (50)	16 (53.3)	17 (56.6)
Treatment received			
Oral antibiotic	20 (100)	28 (93.3)	22 (73.3)
IM antibiotic		2 (6.6)	10 (33.3)
NSAID	10 (50)	11 (36.6)	10 (33.3)
Antihistamine		6 (20)	19 (63.3)
Antipyretic	1 (5)	7 (23.3)	2 (6.6)
Cough syrup	6 (30)	2 (6.6)	1 (3.3)

AURT: Acute upper respiratory tract, URTI: Upper respiratory tract infection, NSAID: Nonsteroidal anti-inflammatory drug, SD: Standard deviation

Table 3: Mean±SD differential blood count analysis of the study patients before and after zinc or zinc+Vitamin A supplementation (*n*=80)

Clinical parameter	Before treatment mean±SD			After treatment mean±SD		
	Group 1 (placebo) *n*=20	Group 2 (Zn) *n*=30	Group 3 (Zn+Vitamin A *n*=30	Group 1 (placebo) *n*=20	Group 2 (Zn) *n*=30	Group 3 (Zn+Vitamin A) *n*=30
Hgb (g/dl)	12.6±1	12.1±1	12.4±0.9	12.7±0.9	12.1±0.9	12.3±0.7
WBC×10^3/mm^3	9.0±4.1	9.2±3.4[a]	9.9±4.1[a]	7.25±2.7	6.6±2.5[a]	7.1±2.7[a]
Neutrophil (staph) (%)	5.1±7.9	3.2±2.9[a]	6.4±5.5[a]	3.3±4.8	1.5±0.9[a]	1.9±1.7[a]
Lymphocyte (%)	33±15.3[a]	39.9±17[a]	41.8±18.4[b]	47.25±11.6[a]	53.3±11.4[a]	49.1±9.5[b]
Monocyte (%)	8.3±3.3	7.4±4.1	5.5±2.5[b]	7.8±3.2	6.4±2.6	7.1±1.5[b]
CRP (mg/L)	14.3±15.4[b]	20.1±28.9[a]	15.2±16.3[a]	5.4±6.8[b]	4.9±9.2[a]	3.7±3.1[a]

[a]Highly significant≤0.01, [b]Significant≤0.05. WBC: White blood cell, CRP: C-reactive protein, SD: Standard deviation, Hgb: Hemoglobin

parameters associated with micronutrients supplementation may help to better understand and compromise malnutrition disease-related morbidity and effectively interrupt vicious infection cycles.

The importance of micronutrients such as zinc and Vitamin A is increasingly appreciated to have the largest impact on respiratory diseases burden among children. Several studies have viewed zinc and Vitamin A supplementation as a beneficial therapeutic option to improve many infectious diseases outcomes; nonetheless, still studies inconsistencies and variability warrant further investigations.[30]

Zinc is an important signaling element that plays a pivotal role in cell-mediated immune functions, inflammation, and oxidative stress. These attractive features make this supplement an appealing therapeutic option for many infections and chronic diseases. This is the rationale behind Zn therapeutic benefits in many disease conditions such as acute infantile diarrhea, acute upper and lower RTIs, acrodermatitis enteropathica, and prevention of age-related macular degeneration.[31] Despite that many governments have now officially introduced routine Vitamin A supplementation programs, still its benefits are inconsistent among trials, especially regarding respiratory morbidity.[32]

Moderate–severe malnutrition patients (weight for age <60% of the WHO/National Center for Health Statistics reference) [26] were excluded from the study to avoid modifying supplement effects. All treatment groups' demographic and clinical characteristics and compliance were similar across groups.

As noted from our results in all patient groups, Hgb was not affected post-zinc or zinc + Vitamin A treatment compared to placebo because determination of CBC with differential count was done at enrolment, and 4 days later of the study, so it was a very short period of time to affect Hgb levels. Theoretically, large zinc doses for prolonged periods of time have been thought to be of concern to cause anemia due to a decreased circulating lipoproteins and diminished copper absorption that should impair iron transportation.[33] However, several clinical trials and meta-analysis results have contradicted this theory and reported zinc supplement as a relatively safe intervention that does not adversely affect

Hgb level.[34,35]

In fact, the decrease in neutrophil count initiated by Zn supplement in this study is in agreement with previous studies that reported a potential Zn antioxidant effect by negatively affecting neutrophils and inflammatory cytokines and their generated reactive oxygen species (ROS) in normal healthy subjects.[36-38]

In addition, lymphocytes count increased in all groups as vast majority 80–90% of RTIs are caused by viruses[39] and lymphocytosis occurs in acute viral infections.[40] The major increase was in zinc group. Zinc treatment significantly improved lymphocytes count in our study. It has been previously reported that zinc supplement increased the number of circulating T-lymphocytes, especially CD4 cells.[41] This may be attributed to zinc directly affecting lymphocytes differentiation, maturation, and proper function. An increased level of lymphocytes apoptosis has been observed in zinc-deficient mice.[42] Similarly, a previous study on pediatric patients with shigellosis showed that only a 2 weeks' treatment course of 20 mg elemental Zn during acute shigellosis increased the lymphocyte proliferation and boosted immune function.[43]

CRP has long been known as an attractive marker of inflammation, as its concentrations increased rapidly within a few hours of infection and even before the incidence of any clinical symptoms.[44] In our study, zinc supplement was associated with significant decrease in CRP, an effect that can be attributed to its potential antioxidant and anti-inflammatory role that has been repeatedly pointed out in several studies. Zn supplement has been associated to be inversely related to the degree of inflammation and CRP levels in hemodialysis patients,[45] diabetic patients,[46] critically ill sepsis patients,[47] HIV patients,[48] and RTIs.[49]

However, when comparing the monocytes percentage values in Zn and Zn + Vitamin A groups, it was highly significant in Zn + Vitamin A group only. This result agreed with a study reported a positive association between Vitamin A stores and production of ROS by stimulated monocytes, suggested greater protection against bacterial infections.[50]

The current results disagree with the previous studies that reported that Vitamin A supplementation had no effect on acute lower RTIs.[51] Other previous studies have debated that Vitamin A may increase respiratory infection adverse events.[52] In contrast, several other studies have shown the beneficial role of Vitamin A added to zinc supplementation in significantly decreasing acute lower respiratory infections.[51,53]

Such controversial outcomes regarding Vitamin A role in respiratory morbidity may be attributed to possible concurrent nutritional deficiency that may impair Vitamin A absorption and utilization and also may be due to the differences in treatment regimens as smaller frequent Vitamin A doses appeared to be more beneficial than once large doses.[54,55] Another explanation for this discrepancy was suggested by other studies that concluded that Vitamin A supplementation was only effective in malnourished children, as it improved their humoral and cellular immune functions and reduced their total morbidity and mortality in several infectious diseases such as measles, diarrhea, and ARTI.[56] Nevertheless, the same intense pharmacological response of the vitamin in well-nourished children may be associated with adverse effects due to a more pronounced inflammatory response.[57]

Regarding disease morbidity, both zinc and zinc + Vitamin A supplementation showed a significant reduction in AURTI and school absence incidences, compared to placebo group. This is in accordance with several other studies that also reported zinc supplement correlation with lower episodes of AURTIs in a highly mentally and physically stressed population such as the United States Air Force Academy.[20] Moreover, zinc supplement has been associated with decreased duration of cold symptoms and incidences[19] and less need for antibiotics in severe infections.[23] Daily zinc supplementation was found to decrease the incidence of diarrhea and ARIs as early as 6 weeks of age.[58]

Possible Limitations of Study

Infants aged 1–9 months and children <2 were not included in our study, besides our data cannot differentiate whether this beneficial influence of Zn was due to previous zinc deficiency or due to direct boosting of the immune system that is independent of zinc depletion as plasma zinc levels were not measured.

CONCLUSION

Adding zinc or simultaneous zinc and Vitamin A supplementation is positively impacted hematological parameters and AURTI disease outcomes in the studied patients. Nonetheless, this study sheds light on the effect of zinc and simultaneous zinc and Vitamin A supplementation intervention in lowering AURTIs burden among children. Practically speaking, the current finding of the study suggests that concurrent zinc or simultaneous zinc and Vitamin A therapy potentially reduces inflammatory markers such as WBC count, neutrophils, and CRP and improved cell-mediated immunity and significantly decreases school absence and AURTIs incidence without affecting Hgb levels. Nevertheless adding Vitamin A significantly increases monocytes percent, as Vitamin A is important regulators of monocytic differentiation and function, which means a greater protection against infections. These findings indicate an important public health impact of zinc and Vitamin A supplementation on children with URTIs, especially in

developing countries, where URTIs are a frequent cause of morbidity in young children which predisposes to the risks of being affected with many diseases such as otitis media, sinusitis, or asthma attacks. Further studies are required to confirm our results and to determine the proper dose for this effect.

ACKNOWLEDGMENTS

The authors would like to thank the staff of Nasser Hospital for their support and help.

REFERENCES

1. Thompson P, Spyridis N, Sharland M, Gilbert RE, Saxena S, Long PF, *et al*. Changes in clinical indications for community antibiotic prescribing for children in the UK from 1996-2006: Will the new NICE prescribing guidance on upper respiratory tract infections be ignored? Arch Dis Child 2009;94:337-40.
2. Hollinghurst S, Gorst C, Fahey T, Hay AD. Measuring the financial burden of acute cough in pre-school children: A cost of illness study. BMC Fam Pract 2008;9:10.
3. Kartasurya MI, Ahmed F, Subagio HW, Rahfiludin MZ, Marks GC. Zinc combined with Vitamin A reduces upper respiratory tract infection morbidity in a randomised trial in preschool children in Indonesia. Br J Nutr 2012;108:2251-60.
4. Kloepfer KM, Lee WM, Pappas TE, Kang TJ, Vrtis RF, Evans MD, *et al.* Detection of pathogenic bacteria during rhinovirus infection is associated with increased respiratory symptoms and asthma exacerbations. J Allergy Clin Immunol 2014;133:1301-7, 1307.e1-3.
5. Yousef FM, Hamed AF. Prevalence of acute respiratory infection and related risk factors in school age children in Egypt: A cross-sectional study. Int J Curr Res Med Sci 2016;2:50-8.
6. Roth DE, Richard SA, Black RE. Zinc supplementation for the prevention of acute lower respiratory infection in children in developing countries: Meta-analysis and meta-regression of randomized trials. Int J Epidemiol 2010;39:795-808.
7. Truong-Tran AQ, Carter J, Ruffin R, Zalewski PD. New insights into the role of zinc in the respiratory epithelium. Immunol Cell Biol 2001;79:170-7.
8. Chapman MS. Vitamin A: History, current uses, and controversies. Semin Cutan Med Surg 2012;31:11-6.
9. Schooling CM, Jones HE. Could child Vitamin A supplementation have long-term health effects? Int J Epidemiol 2015;44:365-6.
10. Walker CF, Black RE. Zinc and the risk for infectious disease. Annu Rev Nutr 2004;24:255-75.
11. McLaren DS, Kraemer K. Manual on Vitamin A deficiency disorders (VADD). World Rev Nutr Diet 2012;103:1-12.
12. Christian P, West KP. Interactions between zinc and vitamin A: An update. Am J Clin Nutr 1998;68:435S-41S.
13. Gulani A, Sachdev HS. Zinc supplements for preventing otitis media. Cochrane Database Syst Rev 2012;4:CD006639.
14. Cuevas LE, Koyanagi A. Zinc and infection: A review. Ann Trop Paediatr 2005;25:149-60.
15. Yakoob MY, Theodoratou E, Jabeen A, Imdad A, Eisele TP, Ferguson J, *et al.* Preventive zinc supplementation in developing countries: Impact on mortality and morbidity due to diarrhea, pneumonia and malaria. BMC Public Health 2011;11 Suppl 3:S23.
16. Sazawal S. Black RE, Ramsan M, Chwaya HM, Dutta A, Dhingra U, *et al*. Effect of zinc supplementation on mortality in children aged 1–48 months: A community-based randomised placebo-controlled trial. Lancet 2007;369:927-34.
17. Aggarwal R, Sentz J, Miller MA. Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: A meta-analysis. Pediatrics 2007;119:1120-30.
18. Prasad AS, Beck FW, Bao B, Snell D, Fitzgerald JT. Duration and severity of symptoms and levels of plasma interleukin-1 receptor antagonist, soluble tumor necrosis factor receptor, and adhesion molecules in patients with common cold treated with zinc acetate. J Infect Dis 2008;197:795-802.
19. Vakili R, Vahedian M, Khodaei GH, Mahmoudi M. Effects of zinc supplementation in occurrence and duration of common cold in school aged children during cold season: A double-blind placebo-controlled trial. Iran J Pediatr 2009;19:376-80.
20. Veverka DV, Wilson C, Martinez MA, Wenger R, Tamosuinas A. Use of zinc supplements to reduce upper respiratory infections in United States air force academy cadets. Complement Ther Clin Pract 2009;15:91-5.
21. Eby GA. Zinc lozenges as cure for the common cold-a review and hypothesis. Med Hypotheses 2010;74:482-92.
22. Nissensohn M, Sánchez-Villegas A, Fuentes Lugo D, Henríquez Sánchez P, Doreste Alonso J, Peña Quintana L, *et al.* Effect of zinc intake on growth in infants: A Meta-analysis. Crit Rev Food Sci Nutr 2016;56:350-63.
23. Mittal P, Kalra P. Serum zinc levels in children 6 months-12 years having tuberculosis. Pediatr Infect Dis 2015;7:36-40.
24. Thornton KA, Mora-Plazas M, Marín C, Villamor E. Vitamin A deficiency is associated with gastrointestinal and respiratory morbidity in school-age children. J Nutr 2014;144:496-503.
25. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, *et al.* Evidence-based interventions for improvement of maternal and child nutrition: What can be done and at what cost? Lancet 2013;382:452-77.
26. Dewey K, Peerson JM, Brown KH, Krebs NF, Michaelsen KF, Persson LA, *et al*. World health organization working group on infant growth of breast-fed infants deviates from current reference data: A pooled analysis of US, Canadian, and European data sets. Pediatrics 1995;96:495-503.
27. Dye C, Mertens T, Hirnschall G, Mpanju-Shumbusho W, Newman RD, Raviglione MC, *et al.* WHO and the future of disease control programmes. Lancet 2013;381:413-8.
28. Osendarp SJ, van Raaij JM, Darmstadt GL, Baqui AH, Hautvast JG, Fuchs GJ. Zinc supplementation during pregnancy and effects on growth and morbidity in low birthweight infants: A randomsied placebo controlled trial. Lancet 2001;357:1080-5.
29. Fu W, Ding LR, Zhuang C, Zhou YH. Effects of zinc supplementation on the incidence of mortality in preschool children: A meta-analysis of randomized controlled trials. PLoS One 2013;8:e79998.
30. Walker CL, Black RE. Zinc for the treatment of diarrhoea: Effect on diarrhoea morbidity, mortality and incidence of future episodes. Int J Epidemiol 2010;39 Suppl 1:i63-9.
31. Tecchio C, Micheletti A, Cassatella MA. Neutrophil-derived cytokines: Facts beyond expression. Frontiers in immunology 2014;5:508.

32. Chowdhury S, Kumar R, Ganguly NK, Kumar L, Walia BN. Effect of vitamin A supplementation on childhood morbidity and mortality. Indian J Med Sci 2002;56:259-64.
33. Hantaweepant C, Chinthammitr Y, Siritanaratkul N. Anemia and neutropenia in copper-deficient patients: A report of two cases and literature review. J Med Assoc Thai 2016;99:732.
34. Mujica-Coopman MF, Borja A, Pizarro F, Olivares M. Effect of daily supplementation with iron and zinc on iron status of childbearing age women. Biol Trace Elem Res 2015;165:10-7.
35. Brown KH, Hess SY, Vosti SA, Baker SK. Comparison of the estimated cost-effectiveness of preventive and therapeutic zinc supplementation strategies for reducing child morbidity and mortality in Sub-Saharan Africa. Food Nutr Bull 2013;34:199-214.
36. McCord MC, Aizenman E. The role of intracellular zinc release in aging, oxidative stress, and Alzheimer's disease. Front Aging Neurosci 2014;6:77.
37. Robson PJ, Bouic PJ, Myburgh KH. Antioxidant supplementation enhances neutrophil oxidative burst in trained runners following prolonged exercise. Int J Sport Nutr Exerc Metab 2003;13:369-81.
38. Bonaventura P, Benedetti G, Albarède F, Miossec P. Zinc and its role in immunity and inflammation. Autoimmun Rev 2015;14:277-85.
39. Schaad U, Principi, N. The management of recurrent respiratory tract infections in children. Eur Infect Dis 2012;6;111-5.
40. George-Gay B, Parker K. Understanding the complete blood count with differential. J Perianesth Nurs 2003;18:96-114.
41. Cvijanovich NZ, King JC, Flori HR, Gildengorin G, Vinks AA, Wong HR, *et al.* Safety and dose escalation study of intravenous zinc supplementation in pediatric critical illness. JPEN J Parenter Enteral Nutr 2016;40:860-8.
42. Sharif R, Thomas P, Zalewski P, Fenech M. Zinc supplementation influences genomic stability biomarkers, antioxidant activity, and zinc transporter genes in an elderly Australian population with low zinc status. Mol Nutr Food Res 2015;59:1200-12.
43. das Graças Vaz-Tostes M, Viana ML, Grancieri M, dos Santos Luz TC, de Paula H, Pedrosa RG, *et al*. Yacon effects in immune response and nutritional status of iron and zinc in preschool children. Nutrition 2014;30:666-72.
44. Harris T. A Critical Analysis of Iron Status Indicators in Three Independent Studies of South African Primary Schhaool children; 2014.
45. Guo CH, Wang CL. Effects of zinc supplementation on plasma copper/zinc ratios, oxidative stress, and immunological status in hemodialysis patients. Int J Med Sci 2013;10:79-89.
46. Khan MI, Siddique KU, Ashfaq F, Ali W, Reddy HD, Mishra A, *et al.* Effect of high-dose zinc supplementation with oral hypoglycemic agents on glycemic control and inflammation in type-2 diabetic nephropathy patients. J Nat Sci Biol Med 2013;4:336-40.
47. Mertens K, Lowes DA, Webster NR, Talib J, Hall L, Davies MJ, *et al.* Low zinc and selenium concentrations in sepsis are associated with oxidative damage and inflammation. Br J Anaesth 2015;114:990-9.
48. Poudel KC, Bertone-Johnson ER, Poudel-Tandukar K. Serum zinc concentration and C-reactive protein in individuals with human immunodeficiency virus infection: The positive living with HIV (POLH) study. Biol Trace Elem Res 2016;171:63-70.
49. Sempértegui F, Estrella B, Rodríguez O, Gómez D, Cabezas M, Salgado G, *et al.* Zinc as an adjunct to the treatment of severe pneumonia in Ecuadorian children: A randomized controlled trial. Am J Clin Nutr 2014;99:497-505.
50. Ahmad SM, Haskell MJ, Raqib R, Stephensen CB. Markers of innate immune function are associated with vitamin a stores in men. J Nutr 2009;139:377-85.
51. Rahman MM, Vermund SH, Wahed MA, Fuchs GJ, Baqui AH, Alvarez JO, *et al.* Simultaneous zinc and vitamin A supplementation in Bangladeshi children: Randomised double blind controlled trial. BMJ 2001;323:314-8.
52. Villamor E, Fawzi WW. Vitamin A supplementation: Implications for morbidity and mortality in children. J Infect Dis 2000;182 Suppl 1:S122-33.
53. Long KZ, Santos JI, Rosado JL, Lopez-Saucedo C, Thompson-Bonilla R, Abonce M, *et al.* Impact of vitamin A on selected gastrointestinal pathogen infections and associated diarrheal episodes among children in Mexico City, Mexico. J Infect Dis 2006;194:1217-25.
54. Rahmathullah L. Reduced mortality among children in southern India receiving a small weekly dose ok vitamin a. Pediatr Infect Dis J 1991;10:346.
55. Benn CS, Aaby P, Arts RJ, Jensen KJ, Netea MG, Fisker AB, *et al.* An enigma: Why vitamin A supplementation does not always reduce mortality even though vitamin A deficiency is associated with increased mortality. Int J Epidemiol 2015;44:906-18.
56. Ruel MT, Alderman H, Maternal and Child Nutrition Study Group. Nutrition-sensitive interventions and programmes: How can they help to accelerate progress in improving maternal and child nutrition? Lancet 2013;382:536-51.
57. Iannotti LL, Trehan I, Manary MJ. Review of the safety and efficacy of vitamin A supplementation in the treatment of children with severe acute malnutrition. Nutr J 2013;12:125.
58. 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. J Nutr 2015;145:2153-60.

How to cite this article: Shaker SM, Fathy H, Abdelall EKA, Said ASA. The effect of zinc and Vitamin A supplements in treating and reducing the incidence of upper respiratory tract infections in children. Natl J Physiol Pharm Pharmacol 2018;8:1010-1017.

Source of Support: Nil, **Conflict of Interest:** None declared.