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Effectiveness of vitamin A supplementation among children under 5 years old in Kazakhstan

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ABSTRACT

Micronutrient sufficiency leads to high rates of morbidity and mortality among children in Kazakhstan. Kazakhstan does not have a program for mandatory vitamin A supplementation of children under 5 years of age. Thus, the aim of this study was to assess the effectiveness of a pilot vitamin A supplementation program among children in Kazakhstan with the ultimate goal of informing future vitamin supplementation efforts. In Akmola and Kostanay regions of Kazakhstan, 529 children (aged 6-59 months) were randomly selected in each region through the local policlinics. In the first step of the study, mothers of the children were surveyed about the health status of their children using a standard data collection tool. Children were supplemented with Vitamin A using oral at a dose of 100,000 IU for children aged 6-11 months and 200,000 IU for children aged 12-59 months. Blood serum samples were collected for determining Vitamin A status. In the second step of the study, mothers were interviewed again about the health status of their children 6 months after the intervention and blood serum samples were collected to assess the efficacy of Vitamin A supplementation program. The number of self reported diarrhea cases and other intestinal infections significantly decreased after the vitamin A supplementation. The number of children with normal level of Vitamin A signficantly increased from before to after the intervention. Data from all participants (n = 529; pre VAS and 501 post VAS) showed that mean serum retinol levels increased significantly post VAS from 30.01 ±0.5 µg/dL to 61.06 ±1.2 µg/dL (p <0.001) Likewise, a significant change was observed in the cases of reported diarrhea between pre-test and post-test assessments (30 vs. 95; p <0.01). The health status of the examined children in the Akmola and Kostanay regions had significantly improved after the vitamin A supplementation and it points to the necessity of implementing Vitamin A supplementation program on the national level. This study has important policy implications for recommending the supplementation program on the national scale.

Keywords: children, awareness, vitamin A, deficiency, prevalence, prevention, supplementation

INTRODUCTION

Deficiency of a number of micronutrients, or "hidden hunger" **[1]**, is widespread in Kazakhstan and is detrimental to the health of the population, especially for mothers and young children **[2]**. Hashizume et. Al. reported that anemia among school-aged children in rural Kazakhstan (Kzyl-Orda region) appears to be related to iron indices and vitamin A status **[3]**. In countries with a VAD prevalence rate of ≥ 20%, it is recommended to supplement children with high doses of vitamin A **[4]**. Vitamin A plays an important role in the processes of reproduction and growth, differentiation of epithelial and bone tissue, maintenance of immunological status and vision function (photoreception) **[5]**.

Vitamin A deficiency (VAD) leads to problems with vision, increased incidences of respiratory, gastrointestinal, skin and genitourinary infections, as well as a significant increase in mortality in children under five years of age from acute respiratory infections, measles and diarrhea **[6]**. VAD reduces immunity and significantly increases morbidity and mortality in children under 5 years of age **[7]**. Vitamin A supplementation programs are useful due to their low cost and high effectiveness in preventing VAD, as well as reducing morbidity and mortality in children aged 6-59 months, and preventing other serious negative consequences of VAD **[6]**.

According to the recommendations of WHO and UNICEF, a vitamin A supplementation program for children under 5 years of age is being widely implemented throughout the world (twice a year with a vitamin A preparation in a dose of 100,000 IU for children 6-11 months and 200,000 IU for children 12-59 months) **[8]**. Consistent with these recommendations, supplementation programs are being implemented in the neighboring republics of Central Asia, including Uzbekistan, Tajikistan and Kyrgyzstan **[9]**.

The aim of this study is to determine vitamin A level before and after the supplementation program in Kazakhstani children with the ultimate goal of informing supplementation policies.

Scientific Hypothesis

The republic still lacks a system of biological monitoring of vitamin A status among children, which reduces the sustainability and reliability of ongoing preventive programs. The implementation of Vitamin A supplementation among children 6-59 month solves this problem.

MATERIAL AND METHODOLOGY

Samples

We recruited a representative sample of 529 out of 3851 potential volunteers (the total population of catchment areas of the polyclinics were working with was 27500 residents at the time of study). Participants aged 6-59 months were recruited through the network of children polyclinics (primary care centers) by reaching mothers, with mothers being surveyed pre and 6 months post the Vitamin A supplementation. For the current survey, our focus is on comparing the conditions before and six months after Vitamin A supplementation. Consequently, control groups were not included in this study. However, for future surveys, considering the potential benefits of incorporating control groups could enhance the research design. By including control groups, we can establish a more robust experimental framework, allowing for a clearer understanding of the specific effects of Vitamin A supplementation, while controlling for external factors that may influence the results. This adjustment in methodology will contribute to a more comprehensive and rigorous analysis in future research endeavors.

Survey and supplementation took place after receiving signed informed consent to participate in the study. The purpose and importance of this study were explained to the mothers. The Health Conditions Questionnaires was the standardized tool used for data collection in this study. Survey tool was translated into Kazakh and Russian languages and was conducted by trained interviewers **[10]**.

Instruments

Serum retinol levels were determined simultaneously using high-performance liquid chromatograph (HPLC) under high pressure according to the method published by Craft et al **[11]**. Used HPLC apparatus "Waters" 2487" with Breese system, USA software.

Laboratory Methods

To determine the content of vitamin A in blood serum, 5 mL of intravenous venous blood was collected by experienced medical workers. Blood was centrifuged at 3000 rpm for 5 min at room temperature. The sera and blood specimens were immediately frozen at -10 °C, kept for 1 week and then transported to Almaty in a portable ice box filled with dry ice. All specimens were kept frozen at -80 °C until analyses.

On the basis of WHO criteria **[12]**, the following serum retinol cut off levels were used **[13]**: in children aged 6-71 months >30 µg/dL (normal level) **[14] [15]**, 20-30 µg/dL (borderline level) **[16]**, and <20 µg/dL (Vitamin A deficiency) **[17]**.

Description of the Experiment

Sample preparation: First stage of the study was conducted from September to December 2012 and second stage from July to October 2013 in Akmola and Kostanay regions. Sample size was estimated taking into account the possible refusal to participate and/or potential 20% drop out rate, with the number of participants increased by 38% over the originally calculated sample size. In the two regions, children were randomly selected from 4 children's polyclinic (2 polyclinics in each region), ensuring recruitment from at least 5 polyclinic catchment areas. Sampling plan assured representation of children from both, rural and urban areas (Table 1).

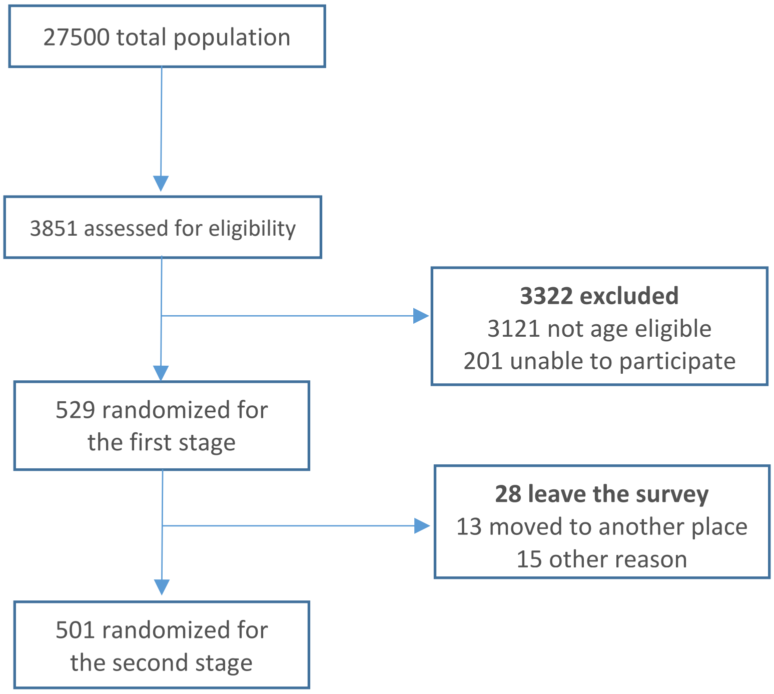

Figure 1 Random sampling of participants.

Number of samples analyzed: 529 participants
Number of repeated analyses: 501 participants
Design of the experiment: This study was carried out under the social order of the Ministry of Health of the Republic of Kazakhstan with the support of the UNICEF office in Kazakhstan. A longitudinal study was conducted in urban and rural areas of Akmola and Kostanay regions. This study was conducted in two stages. In the first stage, mothers of children aged 6-59 months were interviewed about health status of their children using a standardized data collection tool. Children's blood serum samples were collected to assess Vitamin A status. Following the initial assessment, all children were supplemented with oral drops of Vitamin A at a dose of 100,000 IU for children aged 6-11 months and 200,000 IU for children aged 12-59 months. Collection of blood samples and supplementation of children with Vitamin A were conducted by nursing staff. In the second stage, conducted 6 months after the original assessment and supplementation, mothers were interviewed again about the health status of their children. Children's blood serum samples were collected again to assess the efficacy of the Vitamin A supplementation program.

Statistical Analysis

Descriptive statistics were used to analyze the data. We looked at the mean and standard deviation for continuous variables and frequency for categorical variables. Paired t-test and McNemar tests was used to compare the outcomes of each group (pre- and post- Vitamin A supplementation) since the difference between paired samples was normally distributed. All statistical tests were two-tailed, and p values <0.05 were considered as statistically significant. Statistical calculations were performed using IBM SPSS Statistics for Windows, version 29.0.1 (IBM Corp., Armonk, N.Y., USA)

RESULTS AND DISCUSSION

General characteristic of participants

The sample comprised of a total of 529 children 6-59 month, with the majority of participants (89.8%) aged between 12-59 months and the mean age of 33.9 ±13.2 SD in the first stage of data collection. Of these children, 317 (59.9%) were Kazakh, 156 (29.5%) Russian, and 56 (16%) other nationalities/ethnicities, roughly corresponding to the ethnic composition of the Kazakhstan population. 84 (15.9%) of children were breastfed during the first assessment.

Table 1 Characteristics of study participants.

Variables	Frequency	Percentage (%)
Child age		
6-11	54	10.2
12-59	475	89.8
Maternal age		
15-24	115	21.7
25-34	278	52.6
35-49	136	25.7
Residence		
Urban	313	59.2
Rural	216	40.8
Maternal education		
Primary	180	34
Secondary	167	31.6
Tertiary	182	34.6

Maternal knowledge-related characteristics

More than half 289 (54.6%) of the mothers have not heard about medical consequences of vitamin A deficiency, and among 240 (45.4%) mothers who have heard about VAD, one third 83 (34.6%) reported that VAD may cause night blindness. More than half of the participants (55.0%) mentioned eggs and milk as sources of Vitamin A, 31.9% mentioned vegetables and fruits, and 13.0% of the respondents did not mention any food source.

Table 2 Maternal knowledge related characteristics.

Variables	Frequency	Percentage (%)
Have heard about Medical consequences of VAD		
Yes	240	45.4
No	289	54.6
Mention of Medical consequences of VAD		
Night blindness	83	34.6
Weakened immunity	23	9.6
Skin dryness	8	3.3
Growth failure	41	17.1
Other	16	6.7
Not mentioned	69	28.8
Mention of Vitamin A Food source		
Vegetable and fruits	169	31.9
Egg and milk	291	55.0
Not mentioned	69	13.0

Impact of Vitamin A supplementation on health status

The participants could be traced back successfully 6 months after the intervention and 95% response rate was obtained in the second assessment. Table 3 presents the overall differences in the prevalence of different reported health conditions among children 6-59 month pre- and post- receiving Vitamin A supplementation. Significant health status differences of children in the mother's answers were observed between pre- and post- Vitamin A supplementation. Pre- versus postsurvey data were compared by McNemar's test for paired sample. A significant change was detected. Before the Vitamin A supplementation 241 had cold last 6 months and after this number decreased to 136 (95% CI:12.178-54.214, $p<0.01$). Likewise, a significate percentage of change in reporting diarrhea was obtained between pre-test and post-test (30 vs. 95; $p<0.01$). The distribution and changes of the mothers' answer regarding acute respiratory viral infection (ARVI), cardiovascular diseases (CVD), urinary system diseases, ear, nose and throat (ENT) diseases, eye, gastrointestinal tract (GIT) diseases, food allergies, anemia, measles are presented in Table 3.

Table 3 Prevalence of health conditions among children pre and post receiving Vitamin A supplementation.

Pre \ Post	Yes	No	p-value	OR	95% CI
Cold					
Yes	241	136	<0.01*	25.695**	12.178-54.214
No	8	116			
Diarrhea					
Yes	30	95	<0.01*	59.053**	13.866-251.487
No	2	374			
ARVI					
Yes	242	140	<0.01*	32.555 **	13.955-75.945
No	6	113			
CVD					
Yes	1	24	<0.01*	0.960 ***	0.886-1.040
No	0	476			
Urinary system diseases					
Yes	1	8	0.008*	0.889***	0.706-1.120
No	0	492			
ENT					
Yes	16	187	<0.01*	12.663**	2.879-55.702
No	2	296			
Eye diseases					
Yes	5	36	<0.01*	31.806 **	5.960-169.727
No	2	458			
GIT diseases					
Yes	28	97	<0.01*	26.845 **	9.197-78.359
No	4	372			
Food allergies					
Yes	4	61	<0.01*	0.938 ***	0.882-0.999
No	0	436			
Anemia					
Yes	3	79	<0.01*	0.963 ***	0.924-1.005
No	0	419			
Measles					
Yes	0	18	<0.01*	1.004 ***	0.998-1.010
No	2	481			

Note: * McNemar test, binomial distribution; ** For cohort before Vitamin A supplementation; *** For cohort after Vitamin A supplementation.

Data from all participants (n = 529; pre VAS and 501 post VAS) showed that mean serum retinol levels increased significantly post VAS from 30.01 ±0.5 µg/dL to 61.06 ±1.2 µg/dL (p <0.001) (Table 4). The proportion of subjects with serum vitamin A levels above the upper limit of normal (normal range: ≥30 µg/dL) increased from 41.67 µg/dL to 62.66 µg/dL (p <0.001) after Vitamin A supplementation. The indicator of subjects with borderline levels of vitamin A (borderline level: 20-30 µg/dL) increased from 25.33 µg/dL to 63.61 (p <0.001). Total Vitamin A deficiency of serum level increased from 17.57 µg/dL to 27.86 µg/dL (p = 0.008). Vitamin A levels were higher than pre-Vitamin A supplementation in children 6-59 months.

Table 4 Comparison of outcomes measures pre- and post- Vitamin A supplementation.

Measure	Pre-	Post-	t-test (df)	95% CI	p-value*
Normal level of Vit A	41.67	62.66	13.34 (198)	17.88-24.09	p <0.001
Borderline level of Vit A	25.33	63.6	29.06 (187)	35.69-40.88	p <0.001
Vit A deficiency	17.57	27.86	6.27 (3)	1.64-15.51	p = 0.008
Mean of serum retinol	30.01	61.06	30.7 (500)	29.1-33.1	p <0.001

Note:*Paired samples t-test.

The survey findings indicate that vitamin A supplementation has been effective in significantly reducing VAD and leading to improved health of children in the Akmola and Kostanay regions. These findings provide a scientific basis for implementing programs to prevent VAD in children aged 6-59 months, in line with international recommendations. While several food fortifications programs have been implemented in Kazakhstan **[18]**, as of 2024 there is no active vitamin supplementation programs among children under 5 years.

Food fortification is the deliberate addition of essential vitamins, minerals, and nutrients to food during production to enhance nutritional content, addressing and preventing micronutrient deficiencies in populations. Wheat flour manufactured for retail in Kazakhstan undergoes mandatory enrichment with iron-containing vitamins, minerals, and other substances **[19]**, **[20]**. Baker's yeast, bread, bakery goods, and flour-based confectionery items are fortified with iodine preparations, B and E group vitamins, niacin, folic acid, water-soluble K-carotene preparations, and vitamin-mineral supplements **[21]**. Table salt in Kazakhstan undergoes mandatory iodization **[22]**. Fortification is also applied to milk and dairy products, fat-based items, cereal products, and pre-prepared dishes **[23]**. In preschools and other facilities serving children and adolescents, the fortification of foods with vitamin C is also taking place **[24]**. It is important to monitor existing fortification programs to see how they can be improved.

The findings on the impact of vitamin A supplementation on children's health, are consistent with the published literature on VAD prevention by Wirth et al., **[9]**. Foundational study by WHO provides a global perspective, outlining the prevalence of Vitamin A deficiency and setting the stage for interventions **[25]**. Barua et. al., and Harrison et al., explored the intricate mechanisms of Vitamin A metabolism and absorption, enhancing our understanding of its bioavailability **[26]**, **[27]**. One critical aspect of assessing the efficiency of vitamin A supplementation is its impact on child mortality. Numerous studies have demonstrated a substantial reduction in all-cause mortality among supplemented children. For instance, a randomized controlled trial by Smith et al., observed a significant decrease in mortality rates in supplemented groups in low- and middle-income countries, emphasizing the life-saving potential of vitamin A supplementation **[28]**. Amimo et al., and Yu et al., examining the role of Vitamin A in immune responses and its correlation with clinical outcomes broadens our understanding of its potential immune system impact beyond already published health impacts **[29]**, **[30]**. Vijayaraghavan et al., and Mayo-Wilson et al., focus on tackling mineral and vitamin deficiencies in rural African populations while also examining the efficacy of vitamin A supplementation in averting morbidity and mortality among children aged six months to five years. deficiency **[31]**, **[32]**. Vitamin A plays a pivotal role in bolstering the immune system, thereby influencing the incidence and severity of infectious diseases. Recent research, such as the work conducted by Abdelkader et al., suggests a notable reduction in respiratory infections among children supplemented with vitamin A **[33]**. Moreover, studies by Long et al., have explored the relationship between vitamin A supplementation and reduced occurrences of diarrheal diseases, underlining the importance of vitamin A in preventing common childhood illnesses **[34]**. Beyond its role in preventing infectious diseases, vitamin A has been implicated in cognitive development and physical growth. The study conducted by Prado et al., demonstrated positive effects on cognitive development in supplemented children. This aspect is crucial, as cognitive development during the early years lays the foundation for future learning and well-being **[35]**. Ensuring the safety and optimal dosage of vitamin A supplementation is a critical consideration. A systematic review by Soares et al., assessed potential adverse effects and recommended dosage adjustments for different age groups. Balancing the benefits and potential risks is essential for maximizing the positive impact of supplementation while minimizing any unintended consequences **[36]**.

Our results highlight a significant improvement in children's health and a reduction in VAD prevalence after vitamin A supplementation. These findings are also consistent with Villamor and Fawzi studies emphasizing the effectiveness of vitamin A supplementation in reducing VAD and associated health issues, particularly in regions where VAD is prevalent **[37]**. This reduction aligns with the goals of vitamin A supplementation programs, which aim to decrease VAD rates in populations at risk **[38]**. Considering regional perspectives and tailoring interventions to specific contexts is crucial for optimizing the efficiency of Vitamin A supplementation efforts globally **[39]**. McLean et al., and Shah et al., addressing implementation challenges **[40]** and strategies provides insights into optimizing Vitamin A supplementation programs on a global scale **[41]**.

To our knowledge, this was the first formalized effort to assess Vitamin A supplementation in Kazakhstani children. The key strength of this study is its large sample size and random selection of participants that enhances the study's statistical power and the generalizability of its findings. The study considered a diverse range of demographics, including women of various educational backgrounds and children of different ages and health conditions. This diversity allows for a more comprehensive analysis of the population's needs and the impact of vitamin A supplementation. The study compares data before and after vitamin A supplementation, allowing for a clear assessment of the intervention's effectiveness in reducing vitamin A deficiency and improving children's health. And also reports statistically significant increases in children's vitamin A levels and decreases in the prevalence of vitamin A deficiency (VAD) after supplementation. The study follows up after six months of vitamin A supplementation, which is a reasonable duration to assess the effectiveness of the intervention.

The key weakness of this study is lack of a control group for comparison. Having a control group not receiving vitamin A supplementation would have allowed for a more robust assessment of the intervention's effectiveness by controlling for other factors that may influence the outcomes. Self-reported data by caregivers may be subject to recall bias or misreporting. Objective measures or medical records could provide more reliable data in the future investigations. The study assesses the impact of vitamin A supplementation over a relatively short period. Long-term follow-up would be valuable to understand the sustained effects of supplementation on children's health. Also, the study focuses on vitamin A but does not address the broader nutritional status of children, which could also influence health outcomes. A more holistic approach to nutritional assessment might provide deeper insights.

While the international discussion around VAS is vital, more attention should be paid to individual nations where programming choices are decided. Many nations use VAS and other initiatives to enhance VA status without having proof of the national prevalence and severity of VAD, according to our research. Moreover, we have to widely discuss the VAS programs in different countries, to evaluate those programs that really could change the statistics of VAD among their nations, and gradually implement them in other countries as well. Also taking into account socioeconomic differences between urban and rural locations, where vitamin A supply through food may be limited in relatively impoverished rural settings. In rural regions, community education on VAD awareness should be implemented so that caregivers can notice symptoms of VAD in their early stages. Localized techniques for cooking micronutrient-rich meals, as well as availability to vitamin A supplementation, are also crucial in lowering the severity of VAD in those situations. However, because frequent use of high-dose vitamin A supplements is not suggested for all children, these complete dietary methods should be targeted and applied with caution. Critical importance of it especially among infants, taking into account the role of vitamin A in maintenance of the immune system, and susceptibility of infants to different infections that is nowadays the cause of mortality and morbidity of children under 5 years, especially in cases of diarrhea or measles, as well as in visual issues that largely impact nighttime vision (i.e. xerophthalmia). Vitamin A deficiency is still one of the top causes of childhood blindness in underdeveloped nations **[42]**.

Efforts to combat VAD should be integrated into existing health programs, such as maternal and child health services, immunization campaigns, and nutrition education initiatives. This holistic approach maximizes the reach of interventions and ensures a comprehensive focus on child health Efforts to combat VAD should be integrated into existing health programs, such as maternal and child health services, immunization campaigns, and nutrition education initiatives. This holistic approach maximizes the reach of interventions and ensures a comprehensive focus on child health **[43]**.

Future research and interventions should aim to build on the current study's findings and contribute to improved child health and nutrition, particularly in regions where vitamin A deficiency is a significant public health concern. Interventions should be tailored to the specific needs of these high-risk areas, considering socio-economic factors, dietary habits, and cultural nuances. This targeted approach ensures that resources are optimally utilized and interventions are culturally sensitive **[44]**.

The study's findings have several important policy implications for public health, particularly in addressing vitamin A deficiency (VAD) among children aged 6-59 months. By implementing policy recommendations on vitamin deficiency prevention, governments and health authorities can work toward reducing the prevalence of VAD among children and improving overall child health and well-being. Addressing this nutritional deficiency is an important step in achieving better health outcomes for children in affected regions.

CONCLUSION

In conclusion, our findings indicate that vitamin A supplementation has been effective in significantly reducing VAD and leading to improved health of children in the Akmola and Kostanay regions of Kazakhstan. These findings provide a scientific basis for implementing programs to prevent VAD in children aged 6-59 months, in line with international recommendations. Improving the diet, even if it is difficult to achieve in the short term, is of paramount importance because it contributes to improving the overall nutritional status. Fortification of foods with vitamin A has proven to be an effective strategy for reducing VAD in some countries.

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Conflict of Interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Statement:

The study design and questionnaires were preliminarily tested and approved by the Local Ethical Commission of Kazakh Academy of Nutrition (Protocol No. 04, 01.04.2012). The participants provided their written informed consent to participate in this study.

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