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THESIS INTRODUCTION

1. Introduction

Acute Respiratory Infections (ARI) is a disease group caused by bacteries, viruses that acutely damaged a part of or entire of respiratory tract from the ear, nose, throat, lung to pleurisy. ARI is not only common but aslo a leading cause of death in children under 5 years old. According to WHO in 1990, in the whole globe, there are 14 millions deaths in children under 5 years old annually (95% of deaths in developing countries), in which 4 millions children died of ARI.

In 1983, the WHO developed a program against ARI (ARI program), put in practice in Vietnam in 1984 that helped reduce the morbidity and the mortality of ARI but the morbidity and the mortality were still high in this age group. Indonesia, India, Nigeria, Pakistan, and China represented 54% of 138 millions pneumonia globally in 2015. According to Adebola E. Orimadegun et al, there were 1.071 millions deaths in children aged from 1 to 59 months old in Africa died of pneumonia, represented 14.1% of deaths due to all causes. Regarding GBD and Wing Ho Man, the pneumonia mortality rate in children under 5 years old globally was from 10.4-13.1% among common deaths. According to Xin Wang et al, in 2018, in the whole globe, 16% of child deaths was due to lower acute respiratory infection.

Since 2007, Holick FM and Daniel E. Roth et al have considered vitamin D defficiency as "Global epidemics". The study of Khukood Othman Alyahya showed that vitamin D defficiency in children aged from 6-17 years old in Saudi Arabia was 71.1%, in Qatar 61%, in Lyban 52%, and in Iran 29%. There were 66.6% of boys and 78,4% of girls in Kuwait in shortage of vitamin D. According to Italy Consensus in 2018, the global vitamin D difficiency rate was 50%. In Vietnam in 2015, the rate of vitamin D defficiency in the rural area was 61.1% and in the urban area 53.7%.

Current days, vitamin D was found to stimulate the immune system against bacterial infections including ARI. According to Adrian R Martineau et al, Margarita Cariolou et al, Mary Aglipay et al, Zulfiqar A Bhutta et al, vitamin D plays a very important role in reducing the severity, the mortality and the morbidity of ARI.

Because of above reasons, we conducted the study with the following title **"Relationship between vitamin D difficiency and vitamin D supplement efficacy for acute respiratory infection in children under 5 years old in the community"** with the following objectives:

1. Examine the acute respiratory infection rate and the vitamin D difficiency rate in children under 5 years old in An Lao, Hai Phong in 2016

2. Analyse the risk factors of acute respiratory infection and of vitamin D difficiency
3. Evaluate the efficacy of vitamin D supplement for acute respiratory infection in above studied subjects

2. The neccesity of the thesis

Studies of vitamin D supplement to improve the infection status in general and acute respiratory infection in particular have been done for long time but the results were not unanimous and controvery. According to Giuseppe Saggesse et al, in the Italy Consensus of Academy Pediatrics in 2018 showed that the results of meta-analysis about vitamin D trials, observational studies in the world were different. Also according to Giustina A et al, the second international consensus about vitamin D role in fighting infections was not unanimous. According to these opinons, vitamin D efficacy in reducing ARI morbidity rate and the severity of ARI in children under 5 years old were clear that need to be studied more to have concrete conclusions. That is the reason why we conducted this study.

3. Practical significance and new contributions of the thesis

After finishing, The thesis estimated the vitamin D difficiency rate (58.6%) and the acute respiratory rate (36.7%) in children under 5 years old in An Lao, Hai Phong in 2016. These rates contributed to the infection disease and the vitamin D defficiency rate map in children under 5 years old that help protect the child health in An Lao in particular and in Viet Nam in general.

The thesis already determined the strongly relationship between vitamin D defficiency and ARI that was the scientific evidence to carry out the vitamin D supplement for children under 5 years old. Beside, ARI was also associated with child malnutrition, not vaccinated children, and children less than 2 years old. These factors were associated to each other leading to bad consequences including ARI.

The outcome of the vitamin D supplement by taking 500 IU/day during 1 year was the valuable, scientific evidence for clinical doctors who can intervene in children under 5 in larger scale in the conmunity to reduce the rate of ARI. From the reduction of the rate of ARI, it can lead to the reduction of the mortality in the age group.

4. The thesis structure

The thesis consists of 139 pages in which introduction includes 2 pages; chapter 1 (overview) includes 36 pages; chapter 2: (studied subjects) includes 19 pages; chapter 3: (results) includes 39 pages; chapter 4: (Discussion) includes 35 pages; conclusion has 2 pages and recommendation has 1 page.

Chapter 1. Overview

Vitamin D belongs to secosteroid that was soluble in fat, has the function to increase the absorption of calcium and phosphore from the digestive tract. In humans, important substances in the group are vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Cholecalciferol and ergocalciferol were introduced into the body by eating and supplementing. The body can synthesize vitamin D through the skin from cholesterol when the skin expose to the sunlight. The main role of vitamin D was known to increase the absorption and transport of calcium and phosphore from the intestine and the kidney into the blood stream to maintain calcimia and phosphoremia level. Together with the participation of parathyroid hormone and calcitonine, vitamin D maintains the bone development. Nowadays, vitamin D was found to play an important role in many diseases particularly in infection diseases due to its capacity to increase the function of natural immune system.

Acute respiratory infections include sore throat, otitis media, sinusitis, laryngitis, tracheobronchitis, bronchiolitis, and pneumonia. This disease is very common and the leading cause of death in children under 5 years old. Studies showed that vitamin D defficiency became common and globally "epidemic". In the world, the rate of vitamin D defficiency was 50-60%, depending on country and territory. Accỏding to Holick MF et al, vitamin D defficiency and insufficiency occurred when vitamin D level was less than 30 ng/ml. Vitamin D defficiency increase the capacity of suffering from ARI in children under 5 years old. Trials showed that vitamin D supplement was a simple and effective method to reduce the morbidity of ARI. However, according to the international consensus, the role of vitamin D supplement to reduce the rate of ARI in children under 5 years ole among different studies.

In 2009, Yamshchikov A.V et al carried out controlled ramdomized trial of vitamin D supplement in human beings to prevent and treat infection diseases. The outcome showed that it need to further study to affirm the role of vitamin D in treatment of tuberulosis and influenza.

In 2012, Semira Manaseki-Holland et al conducted the trial of high dose of vitamin D supplement and placebo for children aged from 1-11 months. Children taking 100.000 IU vitamin D, placebo very 3 months until 18 months. Author did not regconize the difference in pneumonia rate between 2 groups.

In 2019, Adrian R Martineau et al reviewed controlled ramdomized clinical trials including 11.321 participants aged from 0-95 years old.

Among these participants, 10.933 thousands persons were selected in the study. The author concluded that the vitamin D supplement reduced the likehood of contracting ARI in participants with OR being 0.88 and 95%CI from 0.81 to 0.96) and p<0,001.

In Viet Nam, Mark Loeb and the study group of Vietnamese supplemented vitamin D for studied subjects aged from 3-17 years old to reduce ARI. The result showed that vitamin D supplement did not reduce the morbidity of influenza but it reduced a little bit the morbidity of non influenza in the respiratory tract. Nguyen Xuan Hung supplemented high dose of vitamin D by taking one time during 1 year in children 2-3 years old and found that it reduced significantly the morbidity of ARI.

Chapter 2. Subjects and method

2.1. Studied subjects

Studied subjects included 406 pairs of mothers and children less than 5 years old for the cross-sectional study and 164 children in the same age for intervention study.

2.1.1. Inclusion criteria

Children:

- Born in An Lao, Hai Phong
- Birth day of children was based on birth certificate and registration book
- Familial consensus

2.1.2. Exclusion criteria

Children

- Children with deformities in the digestive tract, in cardiovascular, neurologic system, palsy
- Children with bone metabolic diseases such as cartilage dysplasia, petrified bones, ricket resistant to vitamin D
- Children taking drugs, polyvitamine including vitamin D in the last 2 weeks.
- Children with acute diseases at the time of study
- Children being treated by corticoid or antiepileptic drugs, anti coagulation drugs

Mothers

- Contracting mental disease, memory loss, having capacity to respond questions
- Disagree to participate in the study

2.2. Method

2.2.1. Study design

A cross-sectional study for objective 1 and 2

Controlled community intervention, before and after comparison study for the third objective

2.2.2. Sample size and sampling process

Sample size for baseline survey: 406 pair of mothers and children less than 5 years old

Sampling process: multistages sampling prcess (stage 1: active selection of An Lao; stage 2: ramdomized selection of Truong Tho and An Thang among 15 communes and 2 towns; stage 3: selection of children from 2 communes for the study by systematic ramdom method)

Intervention study: the selection of intervention location by the simple ramdom; the selection of children after the intervetion by systematic ramdon; Truong Tho (intervention) and An Thang (control); Ramdomized selection of 82 children for each group after the intervention to calculate.

2.2.3. Contents, Variable and Indices for the study

2.2.3.1. Contents for baseline study

- to estimate the vitamin D defficiency and insufficiency rate and the rate of ARI

- to describe some risk factors relating to vitamin D defficiency and insufficiency and ARI

2.2.3.2. Contents for intervention study

- At the point T0 (Baseline), children took one drop of vitamin corresponding to 500 IU/day every day during one year. Output information included the vitamin D defficiency and insufficiency rate, ARI rate, height, and weight

- Monthe 6 (T6) (Midpoint): the evaluation of midpoint was done and the indicators were evaluate as followed: weight, height, ARI rate, and vitamin D concentration.

- Termination at month 12 (T12) (Endpoint): children were measured, weighed, estimated the rate of ARI, determined vitamin D level.

2.2.3.3. Variables and indices for baseline study

- Some information about studied subjects
  + Age, gender
  + Weight (kg), height (cm)
  + Maternal profession, income, and education level
- Vitamin D defficiency and insufficiency rate
  + Mean vitamin D concentration
  + Vitamin D defficiency and insufficiency rate regarding age and gender

- ARI rate

+ Common rate of ARI and ARI rate regarding age and gender

+ Kind of disease: upper acute respiratory infectión included otitis media, sore throat; lower acute respiratory infections were larygitis, tracheobronchitis, bronchiolitis, and pneumonia.

+ The distribution of ARI regarding age, gender

+ The distribution of ARI regarding vitamin D defficiency and insufficiency degree

- Some risk factors relating to vitamin D defficiency and insufficiency and acute respiratory infection

+ From children:

++ Gender: boys/girls

++ Agegroup: 0-<12 months, 12 - <24 months, 24 - <36 months, 36-<48 months and 48-<60 months

++ Child order : the first, the second and the third

++ Gestational age: < 37 w and ≥ 37 w

++ Birth weight: <2500 g and ≥ 2500 g

++ Formula milk/exclusively breastfed in the first 6 months: yes, no

+ Vaccination: not completely vaccinated or not vaccinated compared with age: yes/no

++ Children have already suffered from at least one ARI in the last 4 weeks: yes/no

++ Malnutrition: yes/no

++ Not adequate exposure to the sunlight: number of hour/w < 6 vs ≥ 6

+ From monthers:

++ Profession: farmer vs worker, civil officer, housewife, business

++ Mean income: average and lower than ≤ 1.5 millions VND/person/month in rural area and ≤ 2.0 millions VND/person/month in urbain area

++ Low education level : Highschool and lower vs College or higher

- Information after the intervention
  - Age: 0-<12 m, 12 - <24 m, 24 - <36 m, 36-<48 m and 48-<60 m
  - Gender: boys and girls
  - Weight (kg), height (cm)
  - Mean vitamin D concentration ragerding age, gender at T0, T6 and T12 in intervention and control group
  - Rate of ARI in the intervention and the control group
  - Rate of ARI at T0, T6, and T12 in the intervention and in the control group

2.2.4. Information collection

Information collection for the baseline survey included height, weight, interview, entire examination to detect ARI, blood taking for vitamin D concentration, history taking for risk factors of ARI and vitamin defficiency and insufficiency. After the intervention, weight, height, blood taking, interview, entire examination were done again among studies subjects.

2.2.4. Data analysis

- Descriptive analysis:

+ Statistical Indicators: n, mean, SD, rate %.

+ Statistical test: T-test, Mann-Whitney test or ANOVA test to compare means or χ^2 test/Fisher Exact test to compare 2 percentages. The difference was statistically significant when p-value less than 0.05.

-Variate and multinominal Logistic Regression

Statistical test: OR, AOR were analysed were calculated to estimate the relationshio between the vitamin D defficiency and ARI.

If OR<1; there is no relationship of vitamin D deficiency wirh some riskfactors.

If OR= 1.0; there was a no relationship of vitamin D deficiency wirh some riskfactors.

If OR>1 and lies indo among free time time with 95%CI and with lowrer with 95%CI was must bue with differemements'

- Unvariate and multiniminal Logistic Regression

+ Dùng Paired samples T-test, Independent T-test để so sánh chiều cao, cân nặng, và nồng độ vitamin D trước và sau can thiệp, và giữa 2 nhóm sự khác nhau có ý nghĩa khi p<0,05.

+ Dùng χ^2 test để so sánh tỷ lệ NKHHC trước và sau can thiệp.

Chapter 3. Results

3.1. The vitamin D defficiency and insufficiency rate and the acute respiratory infection rate

3.1.1. Information about studied subjects

Table 3.1. Distribution of studied subjects regarding age and gender

Age group (month)	Boys (n,%)	Girls(n,%)	Total (n,%)	p
0-<12	6 (46.2)	7(53.8)	13(3.2)	
12-<24	55(59.8)	37(40.2)	92(22.7)	
24-<36	58(54.2)	49(45.8)	107(26.3)	=0.589
36-<48	62(55.9)	49(44.1)	111(27.3)	
48-<60	40(48.2)	43(51.8)	83(20.5)	
Tổng	221(54.4)	185(45.6)	406(100,0)	

Remark: More boys than girls participated in the study. In group 2, 3, and 4 years old, there were more boys than girls but in group 1 and 5, there were more girls than boys. However, the difference was not statistically significant (p>0.05).

3.1.2. Vitamin D defficiency and insufficiency rate

Table 3.2. Mean vitamin D concentration regarding age group

Age group (month)	Number (n)	Mean (ng/ml) *	SD	p
0-< 12	13	18.20	6.38	0.028
12-<24	92	23.48	5.95	
24-<36	107	24.19	5.86	
36-<48	111	22.91	4.77	
48-<60	83	22.93	4.85	
Chung	406	23.23	5.50	

** One way ANOVA was used to compare mean vitamin D concentration regarding age group*

Remarks: The common neam vitamin D concentration was 23.23 ± 5.50 ng/ml, the highest mean was in the age group 24-<36 months that was 24.19 ± 5.86 ng/ml and the lowest mean of vitamin D concentration in the age group less than 12 months that was 18.20 ± 6.38 ng/ml.

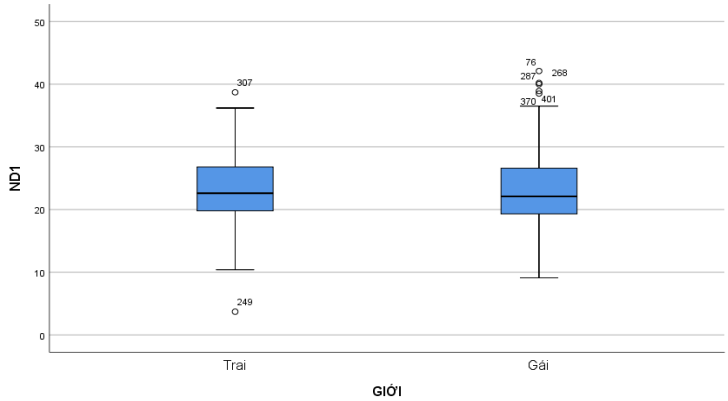


Figure 3.1. Mean vitamin D concentration regarding gender (n=406)

Remarks: Mean vitamin D in boys and in girls was similar. They were 23.32 ± 5.28 ng/ml and 23.13 ± 5.76 ng/ml respectively (p<0.05).

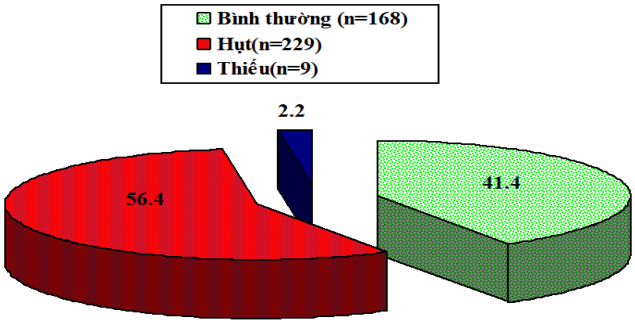


Figure 3.2. Vitamin D defficiency and insufficiency rate (n=406)

Remarks: The vitamin D insufficiency rate was 56.4% and the vitamin D difficiency rate was 2.2%. The vitamin D difficiency and insufficiency were 58.6%.

Table 3.3. The vitamin D defficiency and insufficiency rate regarding age group

Age group (month)	Studied number (n)	Defficient vitamin D number (n)	Percentage (%)	p
0-< 12	13	10	76.9	0.233
12-<24	92	54	58.7	
24-<36	107	54	50.5	
36-<48	111	69	62.2	
48-<60	83	51	61.4	
Tổng số	406	238	58.6	

Remark. The highest rate of vitamin D defficiency in age group less than 12 months (76.9%) then age group 36-<48 months (62.2%), age group 48-<60 months (61.4%), age group 12-<24 months (58.7%) and the lowest rate in the age group 24-36 months (50.5%). The difference of vitamin D rate regarding age group was not statistically significant with p<0. 05.

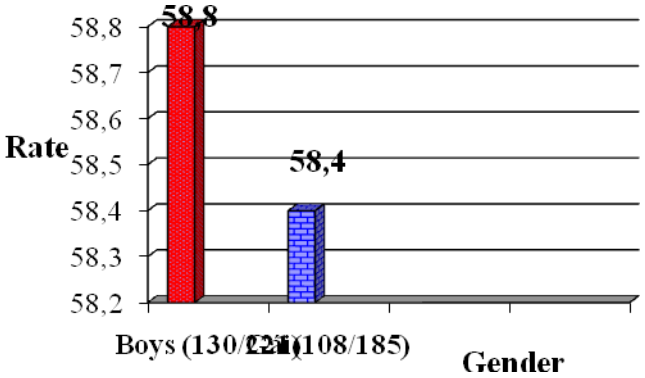


Figure 3.3. The vitamin D defficiency and insufficiency rate regarding gender (n=406)

Remarks: The vitamin D defficiency and insufficiency rate in boys was 58.8% and in girls 58.4%, the difference was not statistically significant with p>0.05.

3.1.3. The acute respiratory infection rate

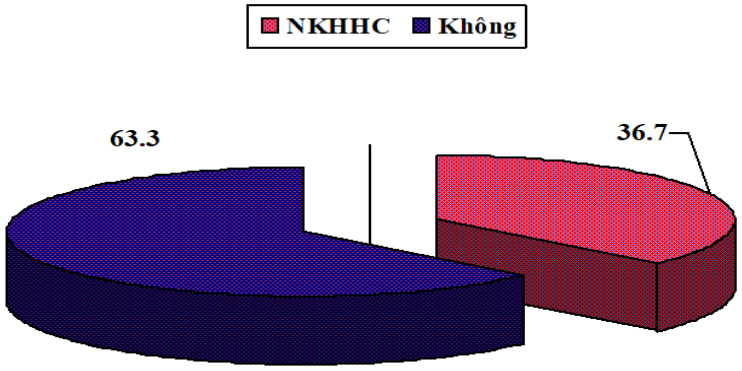


Figure 3.4. The ARI rate in the last 4 weeks (n=406)

Remarks: The acute respiratory infection in the last 4 weeks was 36.7%.

Table 3.4. Kinds of ARI in the last 4 weeks

Kinds of ARI in the last 4 weeks	Number (n)	Percentage (%)
Upper ARI		
Sore throat	149	36.7
Otitis media	34	8.4
Lower ARI		
Laryngitis	64	15.8
Tracheobronchitis	43	10.6
Bronchiolitis	37	9.1
pneumonia	20	4.9

Remarks: Sore throat represented the highest rate 36.7% when pneumonia was the lowest rate 4.7%.

Table 3.5. The ARI rate regarding age group

Age group (month)	Number(n)	Number of ARI (n)	Percentage (%)	p
0-< 12	13	2	15.4	0.007
12-<24	92	22	23.9	
24-<36	107	39	36.4	
36-<48	111	50	45.0	
48-<60	83	36	43.4	
Tổng số	406	149	36.7	

Remarks: Age group 36-<48 m affected the highest rate 45.0% then age group 48-<60 m 43.4%. Age group had the lowest rate was less than 12 m that represented 15.4%. In general, the ARI increased when age groups did. The difference was statistically significant with p< 0,05.

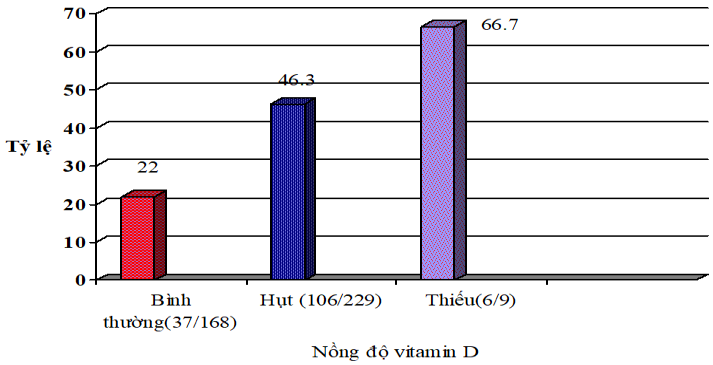


Figure 3.5. ARI rates regarding vitamin D concentration (n=406)

Remarks: There were 6/9 subjects whose vitamin D concentration were less than 20 ng/ml contracting ARI (66.7%). Subjects had vitamin D concentration 20-<30 ng/ml representing 46.3% and the ARI rate was the lowest in the subjects with normal vitamin D concentration (≥ 30 ng/ml) (22.0%). The difference was statistically significant (p < 0,01).

3.2. Some risk factors relating to vitamin D defficiency and insufficiency and ARI

3.2.1. Some risk factors relating to vitamin D defficiency and insufficiency

Table 3.6. Multinominal Logistic Regression of child Risk factors

Vitamin D difficiency / Risk factors	Vitamin D defficiency(n)	No (n)	OR, 95%CI, p (bivariate analysis	AOR, 95%CI, p (mulinominal Logistic Regression
Not adequate vaccination/not vaccinated	133	66	***1.96 (1.31-2.2) 0.001***	***1.64 (1.08-2.49) 0.021***
Adequate	105	102		
Not sunlight exposure	195	120	1.81 (1.13-2.9) 0.012	1.86 (0.96-2.57) 0.740
Yes	43	48		
Formula mild/not exclusively breastfed	39	16	1.86 (1.003-3.56) 0.047	1.52 (0.79-2.89) 0.208
Completely breastfed	119	152		
Birth weight <2500g	35	11	2.46 (1.21-4.99)	2.86 (0,88-3,92)

≥ 2500g	203	157	0.11	0.101
GA<37 w	89	39	***1.96 (1.26-3.08) 0.002***	***1.65 (1.04-2.62) 0.035***
≥ 37 w	149	126		
Malnutrition	37	10	***2.91 (1.4-6.03) 0.03***	***2.62 (1.24-5.57) 0.012***
No	201	158		

Remarks: on the final model, we found that Not adequate vaccination/not vaccinated, GA , 37 w, and malnutrition were related to the lack of vitamin D with AOR 1.64, 1.65, and 2.62 respectively.

Table 3.7. Maternal factors on final model of Multinominal Logistic Regression

Vitamin D difficiency / Risk factors	Vitamin D defficiency(n)	No (n)	OR, 95%CI, p (Bivariate analysis	AOR, 95%CI, p (Mulinominal Logistic Regression
Average income and lower	202	119	***2.31 (1.42-3.56) 0.001***	***2.27 (1.38-3.71) 0.001***
More than average	36	49		
High school or less	228	152	2.4 (1.06-5.43) 0.031	2.22(0.95-5.18) 0.066
College or more	10	16		
Farmer	132	119	1.51 (1.013-2.24) 0.042	1.29 (0,85-1,95) 0.24
Else	36	49		

Remarks. On the maternal factors final model, we found that the lack of vitamin D related to low maternal income with AOR 2.27.

3.2.2. Some risk factors relating to acute respiratory infections

Table 3.8. Child factors on the final model in Multinominal Logistic Regression

ARI / Risk factors	Yes (n)	No (n)	OR, 95%CI, p (Bivariate analysis	AOR, 95%CI, p (Mulinominal Logistic Regression
0-<24 m	26	79	***0.48 (0.29-0,78) 0.0032***	***0.46 (0.27-0.78) 0.004***
24-<60 m	123	178		
Not adequate vaccination/not vaccinated	94	105	***2.47 (1.63-3.74) 0.001***	***1,99 (1.28-3.11) 0.002***
Adequate	55	152		
Formula milk/not exclusively breastfed	28	27	1.97 (1.11-3.49) 0.019	1.55 (0.83-2.91) 0.167
Comletetely breastfed	121	230		
Lack of vitamin D	112	126	***3.15 (2.02-4.91) 0.001***	***2.69 (1,68-4,28) 0.001***
No	37	131		
Malnutrition	29	18	***3.21 (1.71-6.01) 0.01***	***2.89 (1.47-5.72) 0,002***
No	120	239		

Remarks: On the final model, we found that lack of vitamin D, malnutrition, children less than 24 m, and children with not adequate vaccination/not vaccinated were associated with ARI.

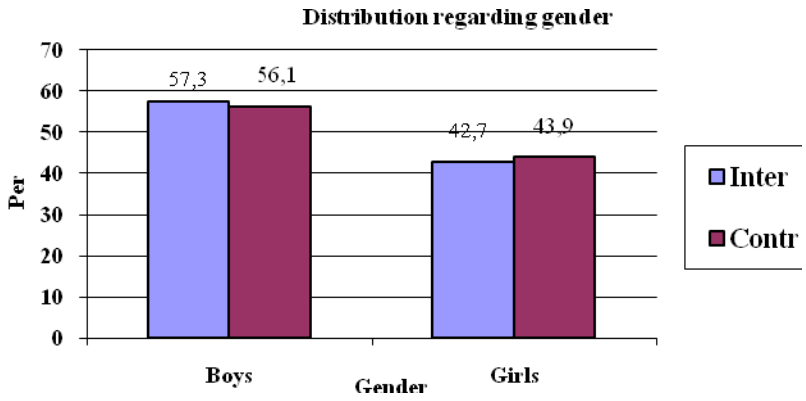
Table 3.11. Maternal factors on final model of the Multinominal Logistic Regression

ARI / Risk factors	Yes (n)	No (n)	OR, 95%CI, p (Bivariate analysis	AOR, 95%CI, p (Mulinominal Logistic Regression
High school and lower	145	235	3.39 (1.47-10.05) 0.020	2.47 (0.81-7.46) 0.116
College and higher	4	22		
Farmer	132	76	***1.51 (1.013-2.24) 0.042***	***1.98 (1.29-3.01) 0.002***
Else	106	92		

Remarks: On the final model of maternal factors we found that ARI was related to maternal profession with AOR 1.98 and p<0.05.

3.3. The efficacy of vitamin D supplement

3.3.1. Information of subjects in the intervention group



Hình 3.3. Distribution of subjects regarding gender in the intervention and in the control groups (n1=n2=82)

Remarks: In the intervention, more boys than girls participated in the study when in the control, more girls than boys did but the difference was not statistically significant with p>0,05.

Bảng 3.10. Distribution of subjects regarding age group in the intervention and in the control group

Age group (month)	Intervention (n1,%)	Control (n2,%)	Total (n,%)	p
0-< 12	3(42.9)	4(57.1)	7(4.3)	0.35
12-<24	12(35.5)	22(64.7)	34(20.7)	
24-<36	23(53.5)	20(46.5)	43(26.2)	
36-<48	24(54.2)	22(45.8)	46(28.0)	
48-<60	20(58.8)	14(41.2)	34(20.7)	
Total	82	82	164	

Remarks : In both intervention and control group, we found that subjects concentrated in age groups 12-<24 and 48-<60 months with the rate 20.7%, 26.2%, 28.0%, and 20.7%. Age group 0-<12 months represented the lowest rate that was 4.3%.

Table 3.11. The efficacy of vitamin D improvement in the intervention and in the control group (ng/ml) (n1=n2=82)

Location	Mean vitamin at T0	Mean vitamin D at T6	Mean vitamin at T12	Mean difference	p
	26.65± 4.63*	30.88± 8.59**	32.19± 4.72***		
Intervention		Mean vitamin D difference at (T0-6)	Mean vitamin D diffrence at (T6-12)	Mean vitamin D at (T0-12)	(0.6)=0.000 (6-12)=0.000 (0.12)=0.000
		4.23 ± 3.96[1]	1.30±3.87[2]	***5.54±0.09[3]***	
Loaction	Mean vitamin at T0	Mean vitamin D at T6	Mean vitamin D at T12		p
Control	27.15± 5.84*	26.88± 6.37**	28.71± 6.94***		(0,6)=0.77 (6-12)=0.121 (0.12)=0.100
		Mean vitamin D difference (T0-6)	Mean vitamin D difference (T6-12)	Mean vitamin D difference (T0-12)	
		0.27 ± 0.17[1]	1.55±1.10[2]	***1.38±1.16[3]***	
p	*0.544	**0.001	***0.000		
Mean difference		3.96±3.79[1]	0,25±2.77[2]	4.16±1.07[3]	

Paired samples T-Test was used to compare mean vitamin D concentration in the intervention and in the control before and after the intervention
** Mean vitamin D concentration at To; ** Mean vitamin D concentration at T6; *** Mean vitamin D concentration at T12*
[1, 2,3] Mean vitamin D concentration defference in the control and in the intervention at T0, T6, and T12.

Remarks:

In the intervention, mean vitamin D concentration increased from 26.65±4.63 ng/ml to 30.88±8.59 ng/ml at T6 and to 32.19±4.72 ng/ml at T12. The mean vitamin D difference at different points after the intervention were statistically significant with p value < 0.01. The mean vitamin D concentration increased from 4.23 to 5.54 ng/ml.

In the control, the mean vitamin D concentration increased from 27.15 ± 5.84 ng/ml to 26.88±6.37 ng/ml at T6 and 28.71±6.94 ng/ml T12 but the mean differences were not big enough to be statistically different with p value 0.77, 0.121, and 0.100 respectively. The mean vitamin D concentration increased from 0.27 to 1.38 ng/ml at T12.

There was a big difference about mean vitamin D of 2 communes at T6 (30.88±8.59 ng/ml and 26.88±6.37 ng/ml, p=0,001) and at T12 (32.19±4.72 ng/ml and 28.71±6.94 ng/ml and p=0,001).

The mean vitamin D concentration in the intervention at T6 and T12 improved better than that in the control at the same points.

Table 3.12. The efficacy of ARI rate in the intervention and in the control after the intervention (n1=n2=82)

Location	ARI rate at T0 (n, %)	ARI rate aT6 (n,%)	ARI rate at T12 (n,%)	Difference	p
Intervention	35* 47.2	25** 30.5	8*** 9.8		
		Reduced ARI rate at (T0-6) (%)	Reduced ARI rate at (T6-12)(%)	Reduced ARI rate at (T0-12)(%)	(0-6) =0.105 (6-12) =0.0009 (0-12) =0.0002
		16,7[1]	20,7[2]	***37,4[3]***	
Location	ARI rate at T0 (n,%)	ARI rate at T6 (n,%)	ARI rate at T12 (n,%)		p
Control	29* 35.4	24** 29.3	17*** 20.7		(0-6) =0.403 (6-12) =0.860 (0-12) =0.086
		Reduced ARI rate at (T0-6) (%)	Reduced ARI rate at (T6-12) (%)	Reduced ARI rate at (T0-12) (%)	
		6.1[1]	8.6[2]	***14.7[3]***	
p	*0.337	**0.864	***0.0206		
Difference		6.1[1]	12.1[2]	22.7[3]	

Chi square was used to compare 2 percentages, there was the difference when p-value less than 0.05.

** ARI rate at T0; ** ARI rate at T6; *** ARI rate at T12*

[1, 2,3] ARI defferences in the intervention and in the control at T0, T6, and T12.

Remarks:

In the intervention, the reduced ARI rate between T0 and T6 was not big enough (p>0.05), between T6 and T12 was big enough (p< 0,001). The reduced ARI rate between T0 and T12 was 37.4% and this difference was big enough (p<0,001).

In the control, the reduced ARI rates at To, T6 and T12 were not big enough with p-values 0.403, 0.86, and 0.086 respectively.

The ARI rates at T0, T6 were not different between 2 communes with p>0,05 and p>0,05 but at T12 there was a significantly different (p<0,05).

Chapter 4. Discussion

4.1. ARI rate and Vitamin D defficiency and insufficiency rate

Table 3.1. showed that there were có 221 (54.4%) boys among 406 studied subjects in which 1 year children represented 3.2%, 2 years children 22.7%, 3 years children 26.3%, 4 years children 27.3%, and 5 years children 20.5%. More boys than girls paticipated in the study because there is a common gender imbalance in Viet Nam.

Table 3.2 was mean vitamin D regarding age group. One year group was 18.2 ng/ml, 2 years grooup 23.48 ng/ml, 3 years group 24.19 ng/ml, 4 years group 22.92 ng/ml, 5 years group 22.93 ng/ml, and common mean vitamin D 23.23 ng/ml. There was a big difference of mean vitamin D concentration among age groups (p= 028). There was not difference of mean vitamin D concentration between gender (Figure 3.1). The vitamin D defficiency and insufficiency rate among age groups (table 3.3) showed that 1 year group was 76.9%, 2 years group 58.7%, 3 years group 50.5%, 4 years group 62.2%, and 5 years group 61.4%. The common rate was 58.6%. there was not difference of vitamin D defficiency and insufficiency rates among age groups (p=0,233). The vitamin D insufficiency rate was 56.4% while the vitamin D defficiency rate was 2.2%, and the vitamin D defficiency and insufficiency rate was 58.6%. The difference was statistically significant. The vitamin D defficiency and insufficiency rate in our study was higher than that of Nguyen Xuan Hung (47.7%) and Tran Thi Nguyet Nga (49.8%). These authors found that there were not difference of the vitamin D defficiency and insufficiency rate between sexes. Our rate was much lower that that of Vu Thi Thu Hien rất nhiều 84%. The difference may be the difference of sample size, age group, and time to conduct the study.

Figure 3.4 showed that the ARI rate was 36.7%. According to age group (table 3.5), we found that the rate was lowest in the age group < 12 months 15.4%, and the highest rate in age group 36-<48 months 45.0%. The difference was statistically significant (p=0,007).

Regarding kinds of diseases we found that sore throat represented the highest rate 36.7%, then otitis media (8.4%), laryngitis 15.8%, bronchitis 10.6%, bronchiolitis 9.11%, and pneumonia 4.9%. Table 3.4 showed that more old children affected ARI than small children.

According to mean vitamin D concentration, we found that children with vitamin D defficicency suffered from the highest rate of ARI 66.7% then children with vitamin D insufficiency were 46.3%.

The results showed that the ARI rate in small children lower than that of old children. It can be explained by the small number of small children or the small children with pneumonia had to be treated at the hospital and were absent when the study was being done. For old children, they contracted milder diseases so they were treated at home or at the health station and paticipated in the study.

4.2. Some risk factors relating to vitamin D defficiency and acute respiratory infection

Some risk factors relating to vitamin D defficiency and insufficiency in the final model of Multinuminal Logistic Regression included not adequate vaccination/not vaccinated (OR=1.64), GA less than 37 weeks (OR=1.65), and malnutrition (OR=2.62). Some risk factors relating to ARI in the final model of Multinuminal Logistic Regression included children less than 24 months old, tháng (OR=0,46), not adequate vaccination/not vaccinated (OR=1.99), vitamin D defficiency and insufficiency (OR=2.69), and malnutrition (OR=2.89) (table 3.6 and 3.8). These results showed that ARI related to the immunodefficiency status due to vitamin D defficiency and insufficiency, malnutrition, not adequate vaccination/not vaccinated, prematurity, and small children less than 24 months old. All weak points can be dealed with vitamin D supplement.

Our results were corresponding to Nguyen Xuan Hung in Hung Yen, to Tran Thi Nguyet Nga in Hai Duong. These authors realized that vitamin D defficiency and insufficiency related to prematurity, acute respiratory infection, not adequate vaccination/not vaccinated, not exclusively breastfed in the first 6 months, early wean and not adequate exposure to sunlight.

Vicka Oktaria et al studied vitamin D defficiency and insufficiency and pneumonia in children in Indonesia in 2021 and found that vitamin D defficiency and insufficiency and pneumonia related to prematurity and malnutrition.

Dang Viet Linh found that ARI related to many risk factors such as prematurity, not exclusively breastfed in the first 6 months, not adequate vaccination/not vaccinated, malnutrition, children less than 12 months old.

4.3. Vitamin D supplement effcacy

Figure 3.3 and table 3.10 showed that studied subjects in both groups were very similar to each other. Regarding gender, in the intervention, boys were 57.3%, in the control, boys were 56.1%. Regarding age group, in the intervention, 1 year age group was 42.9%, 2 years age group was

35.5%, 3 years age group was 53.5%, 4 years age group was 54.2% and 5 years age group was 58.8% (p>0.05).

Vitamin D supplement efficacy:

Table 3.11 showed that at T6 the mean vitamin D concentration in the intervention group gained 4.23 ± 3.96 ng/ml, at T(6-12) gained 1.30 ± 3.87 ng/ml, and after 12 months the mean vitamin D concentration gained 5.54 ± 0.09 ng/ml (all p <0.05).

Int the control group, the mean vitamin D concentration gained 0.27 ± 0.17 ng/ml at T(0-6), 1.55 ± 1.10 ng/ml at (T6-12), and 1.38 ± 1.16 ng/ml (all p >0.05).

At the begining, vitamin D gain in the intervention was higher than that of the control 3.96 ± 3.79 ng/ml, after 6 months 0.25 ± 2.27 ng/ml, and after 12 months 4.16 ± 1.07 ng/ml.

When transversally compared at T6 and T12, the mean vitamin D concentration in the intervention were higher than that of the control with p 0.001 and <0.001 respectively.

Our results were suitable to that of Nguyen Xuan Hung. According to to the author, the vitamin D defficiency and insufficiency rate in the intervention was 20.7%, and this rate before the intervention was 38.9% and the before and after difference was 18.2% with p<0.05.

Heike A Bischoff Ferrari et al in 2006 supplemented one dose of vitamin D more than 1000 IU daily for all adults so that more than 50% of them had their mean vitamin D concentration more than 75 nmol/L. Steven Abrams in 2013 selected 1000 IU Vitamin D supplement daily for all agroups, after 8 weeks of supplement, they found the significant relationship between 1.25 $(OH)_2$Vitamin D concentration and calcium absorption. According to Holick et al in 2008, only when Vitamin D dose increased to 800 IU/daily in 5 months then 25 $(OH)_2$Vitamin D concentration maintained more than 75 nmol/L or 30 ng/m. Nguyen Xuan Hung's study supplemented 200.000 IU/12 months of vitamin D reduced the vitamin D defficiency and insufficiency to 68.64% in the intervention group. Nguyen Xuan Ninh in 2014 supplemted 400 IU of Vitamin D_2 (Ergosterol) fortified in biscuits for primary schoolers 5 days/ week during 4 months, results showed that mean Vitamin D concentration in the intervention higher than that of the control (26.1±6.4ng/ml vs 21.5±3.5ng/mL) (p<0.001). The vitamin D defficiency and insufficiency in the intervention (22.6% and 7.5%) lower than that of the control (59.8% and 19.9%) after 4 months of the intervention.

Table 3.12 was the reduction of ARI rate. At T6 in the intervention reduced 16,7%, last 6 months reduced 20.6%, and after 12 months reduced 37.4%. Except for T(0-6), the reduction of ARI rate was statistically significant compared the point before. In the control group, the reduction rate was 6.1% at T(0-6), 8.6% at T(6-12), and 14.7% at (T0-12), the improvement was not big enough compared the point before (all p>0.05).

When comparing transversally, the reduction rate in the intervention and in the control at T(0-6) and at T(6-12) were not big enough but at T(0-12) the difference was big enough (p=0,0206).

The reduction of ARI rate in the intervention at different points were bigger thant that of the control as followed: 6.1% at T(0-6), 12.1% at T(12,1%), and 22.7% at (T0-12).

Our results were similar to that done oversea or in the country. Firstly, controlled ramdomized clinical trials showed the reduction of ARI rate. The study of Mark Loeb et al in children and adolescents of Vietnam found that the vitamin D supplement reduced the rate of non viral infections.

The controlled ramdomized double blind clinical trials of Manaseki-Holland et al found that 100.000 IU vitamin D dose supplement reduced recurrent ARI in children aged from 1 to 36 months.

The controlled ramdomized double blind clinical trials of Seiji Arihiro et al was done on 223 children with digestive diseases. Children got 500 IU of vitamin D daily. Results showed that vitamin D supplement reduced the ARI morbidity.

Nguyen Xuan Hung and Tran Thi Nguyet Nga supplemented vitamin D for children in age group 2-3 years old in the community. Results showed that the vitamin D reduced significantly the morbidity of ARIs.

Other studies showed the same results as ours. Jaykaran Charan et al studied Meta-analysis of controlled ramdomized clinical trials to evaluate the efficacy of vitamin D supplement in reducing ARI rate. Results showed that the vitamin D supplement rediced the ARI morbidity.

Rashmi Ranjan Das et al conducted the Meta-analysis of 32 studies to compare the results of treatment by using vitamin D and placebo. Vitamin Dose used ranged from 1000 to 100.000 IU in children under 5 years old. Children were supplied one single dose or 5 doses in 5 days, and intervention time was one year. Results showed that vitamin D supplement did improve the ARI rate in childeren under 5 years old.

The research of Hide H.F.Remmelts et al to anwer the question if the vitamin D supplement can reduce the morbidity of pneumonia in the

community. Vitamin D status was the only independent variable for the death with 30 days of pneumonia in the community. Th authors went to conclude that the vitamin D supplement was strongly associated with the prognosis of contracting pneumonia in the community.

After one year of intervention by small dose of vitamin D supplemen, the vitamin D defficiency and insufficiency, and high rate of ARI were statistically improved in the intervention compared with the control.

Conclusion

1. Vitamin D defficiency and insufficiency and acute respiratory infection rate

Vitamin D defficiency and insufficiency rate was 58.6% in which insufficiency rate was 56.4% and defficiency rate was 2.2%. The highest rate was in the 1 year age group 76.9% and the lowest rate was in the 3 years age group 50.5%. The was not difference in vitamin D rate in both sexes.

The acute respiratory infection rate was 36.7%. Upper acute respiratory infection included sore throat 36.7%, otitis media 8.4%; lower acute respiratory infection consisted of laryngitis 15.8%, bronchitis 10.6%, bronchiolitis 9.1%, and pneumonia 4.9%. The ARI was highest in 5 years age group 43.3% and the lowest rate was in 1 year age group 15.4%. ARIs were met most in boys and they increased gradually from 2 to 5 years old.

The high rate of ARIs in subjects with vitamin D defficiency 66.7% and with vitamin D insufficiency 46.3%.

2. Some risk factors relating to vitamin D defficiency and acute respiratory infection

2.1. Factors from children:

Some risk factors relating to vitamin D defficiency and insufficiency on the final model of Multinominal Logistic Regression included not adequate vaccination/not vaccinated (OR=1.64), GA less than 37 weeks (OR=1.65), and malnutrition (OR=2.62). Some risk factors relating to ARI were composed of children less than 24 months (OR=0.46), not adequate vaccination/not vaccinated (OR=1.99), vitamin D defficiency and insufficiency (OR=2.69) and malnutrition (OR=2.89).

2.2. Factors from mothers:

On the final model of Multinominal Logistic Regression, maternal factors relating to vitamin D defficiency anf insufficiency included

average familial income or less (OR=2.27) and some risk factors relating to acute respiratory infection included maternal farmer (OR=1.98).

3. The outcome of acute respiratory infection improvement

After the intervention, mean vitamin D concentration gained 5.54 ng/ml in the intervention group compared with 1.38 ng/ml in the control group, the mean difference was 4.16 ng/ml.

The vitamin D supplement reduced 37.2% of ARI rate in the intervention group compared with 20.7% in the control group. The rate difference was 22,7%.

Reconmendation

1. It need to plan to screen acute respiratory infection and vitamin D defficiency and insufficiency rate early in children under 5 years ols in general and in the community in particular.
2. It need to carry out the oral vitamin D supplement daily to improve the vitamin D defficiency and insufficiency in children under 5 in the community, so reduce the acute respiratory infection rate, contributing to the cause of fighting and preventing children against infection diseases.

THE LIST OF ARTICLES PUBLISHED RELATED TO THE THESIS

1. Nguyen Thi Ngoc Yen, Vu Thi Thuy, Dinh Van Thuc (2021), "Clinical epidemiological features of Vitamin D defficiency in the children under 5 years old at Truong Tho, An Lao, Hai Phong in 2017", Viet Nam Medicine Journal, Number 2, August, page 184-188.
2. Nguyen Thi Ngoc Yen, Vu Thi Thuy, Dinh Van Thuc (2021), "Some risk factors relating to vitamin D defficiency in children under 5 years old at An Lao, Hai Phong in 2016", Viet Nam Medicine Journal, Number 2, August, page 277-280.
3. Nguyen Thi Ngoc Yen, Vu Thi Thuy, Dinh Van Thuc (2021), "The efficacy of vitamin D supplement for acute respiratory infection in children under 5 at An Lao, Hai Phong in 2017, Viet Nam Medicine Journal, Number 1, September, page 102-106