



## Research Article

# Vitamin D and Pneumonia in Children: A Case Control Study

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## Abstract

### Objectives

To evaluate Vitamin D levels and its correlation with severity and outcome of pneumonia in children.

### Design

It is a case-control study.

### Setting

The study was conducted at tertiary care centre from Northern India from June 2013 to June 2014.

### Participants

Fifty children of 1 month to 12 years of age admitted with pneumonia were enrolled as cases. Fifty age and sex matched children without pneumonia were taken as controls.

### Outcome measures

Vitamin D levels were compared between the groups and were correlated with severity and outcome of pneumonia.

### Results

The median (IQR) age of cases and controls was 12 (5,39) months and 12 (5,39) months respectively. Overall, 76 (86.4%) children were Vitamin D deficient. The median (IQR) Vitamin D levels [cases 6.8 (2.0, 14.5), controls 7.3 (4.7, 14.6) ng/ml;  $p=0.362$ ] and proportions of children having Vitamin D deficiency were similar between the groups. Vitamin D levels were not different among children with pneumonia, severe pneumonia, and very severe pneumonia ( $p=0.985$ ). Odds ratio of children with pneumonia being Vitamin D deficient was 3.7 (95% CI: 0.930, 14.770;  $p$ -value 0.066). Vitamin D levels were not correlated with requirement of intensive care management, mechanical ventilation and duration of hospital stay.

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Citation: Jat KR, Kaur J, Guglani V (2016) Vitamin D and Pneumonia in Children: A Case Control Study. J Pulm Med Respir Res 2: 004.

Received: March 3, 2016; Accepted: April 16, 2016; Published: May 02, 2016

## Conclusion

Majority (86.4%) of children were Vitamin D deficient. Vitamin D levels were not different in cases and controls and were not related to severity and outcome of pneumonia.

The study is registered with Clinical Trials Registry of India (Reg. No: CTRI/2013/09/004021).

**Keywords:** Hospital stay; Pneumonia; Vitamin D

## Introduction

Pneumonia is one of the most common causes of morbidity and mortality in children worldwide. In world, about 150 million children are affected by pneumonia annually [1]. There are about two million deaths annually due to pneumonia in children five years of age [2]. In India, about one-fifth of under-five mortality is attributed to pneumonia [3].

There are numerous risk factors for pneumonia in children e.g., malnutrition, poverty, ethnicity, incomplete vaccination, smoke exposure, and underlying diseases like bronchopulmonary dysplasia and congenital heart diseases [4,5]. Despite interventions to control some or more of these factors, pneumonia continues to be a major threat to child health. There is growing interest to identify other risk factors that may contribute to incidence and severity of pneumonia.

Vitamin D had many functions other than bone metabolism. Recently, Vitamin D is found to have anti-infective property through modulation of innate immune system [6,7]. Vitamin D enhances the expression of Vitamin D Receptors (VDR) and increases production of cathelicidin and beta-defensin-2 peptides which acts through toll-like receptors to elicit antimicrobial function against infections [8-13]. Vitamin D also regulates phagocytosis dependent and antibody-dependent macrophages which protect from respiratory infections [14]. In Vitamin D deficiency, there is decreased expression of VDR resulting in impaired clearance of microbes and uncontrolled inflammation that leads to more lung damage with impaired oxygenation. Vitamin D levels are correlated with respiratory infections. Low Vitamin D production during winter season may be one of the reasons for increased respiratory infections during winter [15,16]. The hospitalization rate for children with acute respiratory infections was also correlated to skin pigmentation, one of factor determining Vitamin D production in human body [16].

Vitamin D is associated with risk and severity of pneumonia in various studies from world. Higher maternal Vitamin D levels were associated with lower risk of pneumonia in one study [17] but not in other study [18]. In observational studies from Iran [19], Kuwait [20], Egypt [21], Ethiopia [22] and Jordan [23] children with rickets had higher risk of pneumonia compared to children without rickets. In case-control studies, mean Vitamin D levels were significantly lower in children with pneumonia compared to controls [13,24-26]. There are very limited studies from India. We could find only one study from Indapur, India in 2004, where higher Vitamin D levels were associated with lower risk of pneumonia [27]. The study did not assess correlation between Vitamin D levels and outcome of pneumonia [27]. The available studies had mixed results and Vitamin D levels may vary according to regions, therefore, it is worthy to conduct more

studies on Vitamin D and pneumonia. If Vitamin D is found to have correlated with pneumonia in children, further studies with emphasis on appropriate method for correction of Vitamin D deficiency may be considered. Thus, this study was planned to assess difference in Vitamin D levels in children with pneumonia and without pneumonia and to correlate Vitamin D levels with severity and outcome of pneumonia.

## Methods

This case-control study was conducted at tertiary care centre from Northern India from June 2013 to June 2014. We enrolled 100 children in the study as per feasibility and available funds. We enrolled 50 children with pneumonia as cases and 50 children without pneumonia as controls. Selection of cases: Children of 1 month to 12 years of age admitted with pneumonia were taken as cases. Pneumonia was defined as World Health Organization (WHO) criteria [28] i.e., presence of tachypnea (respiratory rate of more than 60, more than 50 and more than 40 per minute in children up to two months of age, between 2 month to 12 months and between 1 year to five years of age respectively) with or without chest retractions. In children above 5 years of age, respiratory rate of more than 30 per minute was considered tachypnea. Severity (pneumonia, severe pneumonia and very severe pneumonia) of cases was assessed as per WHO criteria [28]. Children with asthma and tuberculosis were excluded from study. Selection of controls: Children admitted for reasons other than respiratory symptoms and requiring blood sampling were taken as controls. Controls were matched with cases by sex and age ( $\pm 2$  months one year and  $\pm 6$  months above one year of age). Ethics committee approval was taken before commencing the study. Parent's informed consent was taken before enrolling children into study. Demographic, clinical and laboratory data were collected in predefined data collection performa for each child. Cases were managed as per prevailing protocols of hospital by attending physician. Outcome of cases was recorded as: time to resolution of pneumonia (normal respiratory rate for age, no retractions, no oxygen requirement, and feeding well), duration of hospital stay and final outcome (discharge or mortality). Primary outcome was difference in mean Vitamin D levels between cases and controls. Secondary outcome included: proportion of children with Vitamin D deficiency, insufficiency and sufficiency between cases and controls, and relation of severity and outcome of cases with Vitamin D levels.

Venous blood samples were collected from both cases and controls and were used to measure serum 25[OH]D levels by Chemiluminescence assay. Serum 25[OH]D levels of less than 20 ng/ml (50 nmol/L), between 20-30 ng/ml (50-75 nmol/L), and levels of 30-80 ng/ml (75-200 nmol/L) were considered Vitamin D deficiency, insufficiency and sufficiency respectively [29-32].

## Statistical methods

We presented continuous variables as mean $\pm$ SD for normally distributed data and as median (IQR) for skewed data and dichotomous data as percentage. The continuous data were compared between the groups using student's t test for normally distributed data and Mann-Whitney test for data with skewed deviation. The dichotomous data were compared using chi-square test. Correlation between duration of hospital stay and Vitamin D levels was calculated using Pearson's coefficient correlation. Finally, odds ratio was calculated for children with pneumonia being Vitamin D deficient. Statistical analysis was done using SPSS Windows software, version 16. P value of less than 0.05 was considered as statistically significant.

## Results

We enrolled a total of 100 subjects: 50 cases and 50 controls. Demographic profile of cases and controls is shown in (Table 1). Age, male/female ratio, month of enrolment, residence, and other demographic parameters were similar among the groups (Table 1). The majority of control subjects had central nervous system problem (seizure, meningitis) or gastrointestinal problems (diarrhea, vomiting).

Parameters		Cases (n=50)	Controls (n=50)	P value
Age (months) median (IQR)		12 (5, 39)	12 (8, 48)	0.537
Male: Female		31:19	31:19	1.000
Month of enrolment	February	13	3	0.070
	March	7	8	
	April	7	11	
	May	17	17	
	June	6	11	
State of residence	Haryana	13	24	0.133
	Chandigarh	19	10	
	Punjab	11	11	
	Uttar Pradesh	2	2	
	Himachal Pradesh	3	1	
Other		2	2	
Number of siblings (median, IQR)		1 (1, 2)	2 (1, 3)	0.089
Duration of exclusive breast feeding (months); median, IQR		6 (4, 6)	6 (6, 8)	0.143
Number of children with clinical rickets		07	10	0.266
Number of children having complete immunization		46	42	0.525

Table 1: Demographic parameters between cases and controls.

Vitamin D levels were not available for 12 patients (5 cases and 7 controls) due to inadequate sample or spilling during processing. Median (IQR) Vitamin D levels for all participants were 6.9 (2, 14.5) ng/ml with a minimum of 2.0 ng/ml to maximum of 40.9 ng/ml levels. Overall, 76 (86.4%), 8 (9.1%), and 4 (4.5%) children were Vitamin D deficient, insufficient and sufficient respectively. A total of 17 (7 cases, 10 controls) children had clinical rickets and difference between cases and controls was not statistically different (Table 1). The Vitamin D levels were not different between cases and controls (Table 2). Similarly, proportions of children having Vitamin D deficiency were similar among the groups (Table 2). Odds ratio of children with pneumonia being Vitamin D deficient and Vitamin D deficient or insufficient was 3.7 (95% confidence interval: 0.930, 14.770; p-value 0.066) and 3.3 (95% confidence interval: 0.330, 33.024; p-value 0.355) respectively. Hemoglobin levels were also similar between the groups (Table 2).

Calcium, phosphate and alkaline phosphatase levels were similar between cases and controls (Table 2). The levels were categorized as normal, increased or decreased based on laboratory values provided by Nelson textbook of Pediatrics (19<sup>th</sup> Edition) and again there was no difference among groups (Table 2).

Among cases; 24 (48.0%), 16 (32%), and 10 (20%) children had pneumonia, severe pneumonia, and very severe pneumonia respectively. The median (IQR) Vitamin D levels in three category of pneumonia severity were 6.7 (2.0, 14.6), 8.6 (2.0, 11.8), 6.3

Parameters		Cases (n=50)	Controls (n=50)	P value
Vitamin D levels (ng/ml); median, IQR		6.8 (2.0, 14.5)	7.3 (4.7, 14.6)	0.362
Hemoglobin (gm%); mean±SD		9.6±2.3	9.5±2.9	0.827 (95% CI: -1.174, 1.463)
Calcium (mg/dl); mean±SD		9.4±1.7	8.8±1.8	0.106 (95% CI: -0.125, 1.295)
Phosphate (mg/dl); mean±SD		4.7±1.1	4.6±1.1	0.679 (95% CI: -0.349, 0.534)
Alkaline phosphatase (IU/L); median, IQR		162 (127, 238)	204 (137, 274)	0.302
Vitamin D status*; n (%)	Deficient (<20 ng/ml)	42 (93.3%)	34 (79.1%)	0.150
	Insufficient (20-30 ng/ml)	2 (4.4%)	6 (14.0%)	
	Sufficient (>30 ng/ml)	1(2.2%)	3 (6.9%)	
Calcium levels (n=cases 49, control 47)	Normal	25 (51.0%)	32 (68.1%)	0.087
	Hypo	18 (36.8%)	14 (29.8%)	
	Hyper	06 (12.2%)	1 (2.1%)	
Phosphate levels (n=cases 49, control 47)	Normal	38 (77.6%)	40 (85.1%)	0.523
	Hypo	8 (16.3%)	6 (12.8%)	
	Hyper	3 (6.1%)	1 (2.1%)	
Alkaline phosphatase levels (n=cases 49, control 45)	Normal	28 (57.1%)	30 (66.7%)	0.615
	normal range	16 (32.7%)	12 (26.7%)	
	Above normal range	5 (10.2%)	3 (6.7%)	

\*Vitamin D levels could not be assessed in 5 cases and 7 controls.

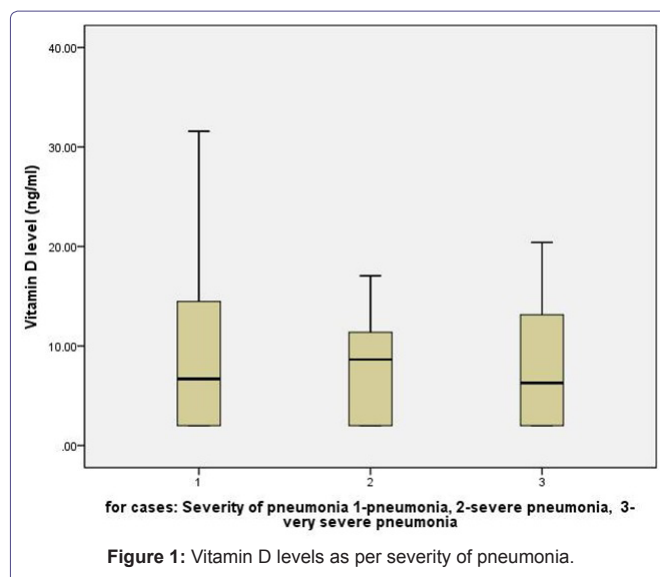
**Table 2:** Laboratory parameters between cases and controls.

(2.0, 13.7) ng/ml respectively (p=0.985, Kruskal Wallis Test). Thus, Vitamin D levels were not different in children with increasing severity of pneumonia (Figure 1). Thirteen (26%) children among cases required intensive care management and four (8%) children required mechanical ventilation. Again, Vitamin D levels were not different in children who required intensive care management and/or mechanical ventilation compared those who did not require it. There was no mortality among enrolled participants. Finally, duration of hospital stay among cases had no relation with Vitamin D levels (Pearson Correlation -0.082, p-value 0.739).

## Discussion

The study revealed that majority of children admitted to a tertiary care center were Vitamin D deficient. In this study only 4.5% children were Vitamin D sufficient. Children admitted with pneumonia and admitted with diseases other than pneumonia had similar Vitamin D levels. Among cases, Vitamin D levels were not associated with severity of pneumonia, requirement of intensive care management/mechanical ventilation and duration of hospital study.

The previously reported case-control studies on Vitamin D and Lower Respiratory Tract Infection (LRTI) in children are shown in (Table 3). Karatekin et al., [13] compared neonates admitted with ALRI in NICU to healthy neonates and found that Vitamin D levels were significantly lower in neonates with ALRI (9.12±8.88 v/s 16.33±13.42 ng/ml; p=0.011) and Vitamin D levels <10 ng/ml were more likely to develop ALRI (OR: 4.25; 95% CI 1.058-17.070; P=0.041). MacNally et al., [24] compared children of less than 5 years of age admitted with pneumonia/bronchiolitis to patients without respiratory



symptoms and found no difference in mean Vitamin D levels between two groups (81±40 v/s 83±30 nmol/L; p=0.71) but the cases requiring PICU admission had significantly lower Vitamin D levels compared to both controls and those admitted to ward. Muhe et al., [25] compared children of less than 5 years of age admitted with pneumonia to those admitted without pneumonia and there was 13-fold higher incidence of rickets among children with pneumonia than controls (13.37 [95% CI 8.08-24.22], p<0.001). Oduwole et al., [33] did not observe difference in Vitamin D levels in children of 2 months to 5 years of age admitted with pneumonia compared to those without pneumonia (104±59 v/s 130±107 nmol/L; p>0.05). Roth et al., [26,34] reported no difference in Vitamin D levels in children of 1 month to 2 years of age admitted for pneumonia compared to controls in the study conducted at Canada [34] but Vitamin D levels were significantly lower in children with pneumonia in the study conducted at Bangladesh [26]. Wayse et al., [27] from India observed significantly lower Vitamin D levels in children of 2 months to 5 years of age with severe pneumonia compared to healthy controls (22.8, 95% CI 21.0-24.7 v/s 38.4, 95% CI 34.2-43.1 nmol/l; p<0.001). There are few Randomized Controlled Trials (RCTs) evaluating the effect of Vitamin D supplementation in Lower Respiratory Tract Infection (LRTI) in children [35-38]. All except one [38] RCT concluded that Vitamin D supplementation was not beneficial in preventing or treating LRTI in children.

There may be several reasons for Vitamin D being similar among cases and controls in present study. First is overall high prevalence of Vitamin D deficiency among studied children; a large proportion of both case and controls were Vitamin deficient. Secondly we took admitted children without pneumonia as controls instead of healthy controls. As Vitamin D had anti-inflammatory and anti-infective properties and children with other diseases may have Vitamin D deficiency also. We did this intentionally to evaluate the role of Vitamin D in pneumonia specifically; therefore, we wanted cases and controls to be similar in almost all aspects except pneumonia. The ideal study to see association between Vitamin D and pneumonia should measure Vitamin D at birth and than at regular intervals and to follow children for development of pneumonia; but we could not do this because of lack of funding.

The strength of study is age and sex matched controls and prospective study. One limitation of study is lack of healthy controls.

## Conclusion

Majority of children admitting to a tertiary care center in north India are Vitamin D deficient. Vitamin D levels are not different in children with pneumonia as compared to children without pneumonia. Vitamin D levels were not related to severity and outcome of pneumonia among cases.

The trial is registered at Clinical Trial Registry of India (CTRI) with registration No. CTRI/2013/09/004021.

**Conflict of Interest:** None.

## Ethics Committee Approval

The study was approved by Institute's ethics committee.

## Acknowledgement

We acknowledge Dr. SK Kabra and Dr. Rakesh Lodha (both from Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India) for their intellectual input in final manuscript.

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