

# Vitamin D intake in young children with acute lower respiratory infection

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## ABSTRACT

**Objective:** To determine if vitamin D intake is associated with acute lower respiratory infections (ALRI) in children.

**Methods:** The vitamin D intakes of children younger than 5 years of age admitted to hospital with either bronchiolitis or pneumonia were compared to an unmatched control group of the same age without respiratory infection. Caregivers of 197 children completed a questionnaire collecting information on demographic variables, ALRI risk factors and diet. Associations of ALRI with vitamin D intake and other ALRI risk factors were determined.

**Results:** The mean vitamin D intake of children with ALRI was 48 IU/kg/d compared to 60 IU/kg/d in the control group. When controlling for age, ethnicity, socio-economic status, northern residence, breastfeeding, immunizations and smoking contact, children with a vitamin D intake of less than 80 IU/kg/d were greater than 4 times more likely to have ALRI compared to children with a vitamin D intake exceeding 80 IU/kg/day (OR 4.9, CI: 1.5, 16.4).

**Conclusions:** A higher vitamin D intake than currently recommended might be needed to offer protection against diseases such as ALRI. Increased vitamin D supplementation could have important public health consequences, as bronchiolitis and pneumonia are the most common reasons for hospitalization in young children.

## KEY WORDS

Bronchiolitis; pneumonia; pediatrics; vitamin D

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## Introduction

Acute lower respiratory infection (ALRI), such as pneumonia and bronchiolitis, is the leading cause of mortality worldwide in children less than age 5 years and represents the most common reason for hospital admission of children within this age group (1,2). Risk factors for the development of ALRI include low birth

weight, non-exclusive breastfeeding, incomplete immunization, indoor air pollution, crowding, parental smoking, and chronic disease (3). It is also hypothesized that the reduction of ultraviolet-B (UVB) radiation exposure during winter is associated with decreased vitamin D production that could account partly for the increased prevalence of ALRI during winter months (4).

Vitamin D insufficiency has been implicated in a number of immune related illnesses including multiple sclerosis, type 1 diabetes, and cancer (5,6), as well as respiratory diseases such as asthma (7-9). In developing countries there is an association between the risk of ALRI and both rickets and subclinical vitamin D deficiency in children (10-14). The same association has not been demonstrated elsewhere, but vitamin D deficiency has been linked to ALRI severity in Canada and the Middle East (15,16). This variability could be secondary to differences in study population and design. Additionally, serum 25 hydroxy vitamin D is likely influenced by acute illness and medical intervention, perhaps making it a less reliable measure of pre-illness vitamin D status (17,18).

No potential conflict of interest.

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Table 1. ALRI Case Definitions.

Diagnosis	Criteria
Pneumonia	Patient under 5 years Temperature > 38 °C Consolidation on chest radiograph Tachypnea*
Bronchiolitis	Patient under 2 years of age Absence of consolidation on chest radiograph <sup>†</sup> Audible wheeze and/or crepitation on auscultation Tachypnea*

\*Respiratory rate of 60 breaths per minute for children aged 0-2 months, 50 breaths per minute for children age 3-12 months, 40 breaths per minute for children aged 13-60 months; <sup>†</sup>Radiograph interpreted independently by two physicians.

Vitamin D (cholecalciferol) is either produced in the skin through UVB radiation or absorbed via the intestine following dietary intake. Given the uncertain reliability of 25(OH)D levels during illness, the objective of this analysis was to determine if vitamin D intake is associated with ALRI during the winter months, when UVB exposure is low. The vitamin D intake of children hospitalized with pneumonia or bronchiolitis was compared to an unmatched control group in the same age range without ALRI. This data was collected as part of a larger study examining vitamin D intake, serum 25(OH) levels and ALRI (15).

## Materials and methods

### Subjects and case definition

Participants were recruited at the Royal University Hospital, Saskatoon, Saskatchewan, Canada from November 2007 to May 2008. Potential study participants included patients less than age 5 years admitted with a diagnosis of either bronchiolitis or pneumonia. These were defined by clinical and radiographic criteria (Table 1). The control population comprised a convenience sample of children less than age 5 years without respiratory symptoms who were receiving care at the Royal University Hospital's ambulatory, emergency or in-patient units. There were no exclusion criteria. The University of Saskatchewan's Biomedical Research Ethics Board approved the study protocol.

### Demographic and questionnaire information

A research nurse or recruiting physician recorded date of

enrollment, age, sex, and medication utilization obtained from health records. At enrollment, caregivers were asked to complete a questionnaire documenting the presence of known ALRI risk factors including: cigarette smoke exposure, ethnicity, breastfeeding history, immunization status, daycare attendance, history of prematurity, birth weight and co-morbid disease. Ethnicity was self-reported as Caucasian, Aboriginal/Métis, Black, Asian or Other. Adequate breastfeeding was defined as having been breastfed for at least 6 months. An incomplete immunization status was defined as none or partial vaccination in children over 2 months of age. Prematurity was defined as birth at a gestational age less than 36 weeks. As an indicator of socioeconomic status, the household person-to-bedroom ratio was calculated as previously described (19). Caregivers also provided their postal code, from which the first three characters were used to categorize the region of residence as northern Saskatchewan (latitude 53 to 59 degrees) or southern Saskatchewan (latitude 49 to 52 degrees).

Daily vitamin D intake was estimated using a food frequency questionnaire; parents reported their child's dietary intake of milk, fish, egg and supplements in the week before enrolment. Daily vitamin D intake from milk was calculated using both the quantity and type of milk. Concentrations of vitamin D were assigned at 40 IU/L for breast milk, 500 IU/L for formula, 400 IU/L for soy and cow milk, 50 IU per egg, and 250 IU for a serving of fish (20-23). For those breastfed children without a known quantity of milk intake, the participant's weight was used to approximate a daily maintenance fluid allotment. For those children who were taking a supplement containing vitamin D, the amount of vitamin D in the supplement was utilized; when the brand of supplement was not known a



Table 2. Diagnosis or presenting complaint for study participants.

Study Group	Diagnosis	(n)	(%)
<b>ALRI</b>			
	Bronchiolitis	55	27.9
	Pneumonia	50	25.4
<b>Control</b>			
	Gastroenteritis	16	8.1
	Pyelonephritis	15	7.6
	Apparent life threatening event	5	2.5
	Jaundice	5	2.5
	Fever of unknown origin	5	2.5
	Healthy	5	2.5
	Infant of Hepatitis C mother	4	2.0
	Trauma	2	1.0
	Rash of unknown origin	2	1.0
	Immune thrombocytopenia	4	2.0
	Cellulitis	2	1.0
	Type I diabetes	2	1.0
	Seizure disorder	2	1.0
	Pyloric stenosis	2	1.0
	Other (separate diagnoses)	21	10.7

value of 400 IU was assigned. As it has been proposed that vitamin D requirements might change with age, the vitamin D intake of participants was calculated as IU/kg (24).

#### Sample size calculation and statistical analysis

The sample size was estimated using a comparison of means, and 10 IU/kg was chosen as the minimum detectable clinically significant difference in vitamin D intake between ALRI and control groups. A standard deviation of 20 IU/kg was conservatively estimated based on the National Health and Nutrition Examination Survey (25). When setting the alpha error at 0.05 and the power at 0.9, a sample size in excess of 85 subjects per group was calculated.

Data were recorded in a computerized database (Statistical Package for the Social Sciences (SPSS) Version 18, Chicago, IL). All data collected over the six month period were anonymized for the purposes of this study. SPSS was used for data analyses. Results are presented as frequencies; percentages for categorical variables or means with standard deviations (SD) for continuous variables for cases and controls separately. Differences in proportions were assessed by means of the

2-tailed Fisher exact test/Chi-square analysis. A bivariate logistic regression analysis was conducted to determine the association between vitamin D intake and ALRI. Based on the model building procedure, univariate variables with  $P < 0.20$  were selected for the multivariate model. For comparisons, odds ratio (OR) and 95% confidence interval (95% CI) were calculated.

## Results

At the end of the 6-month study period, the parents and caregivers of 197 children consented to participate (105 ALRI, 92 Control). The participation rate was 95%; one ALRI subject who met inclusion criteria refused to participate and of the 93 control patients who were approached, one declined to consent. Seventeen of those who consented did not fully complete their questionnaire (8 ALRI, 9 Controls) but any available data was used in the analysis. Among the 105 ALRI cases, 55 had bronchiolitis and 50 had pneumonia. Among these, 16 (15.5%) had disease severe enough to require admission to the Pediatric Intensive Care Unit. The diagnoses or presenting complaints for the control group participants are shown in Table 2. Of the 92



control subjects, 48 were recruited from the inpatient ward, 31 from the emergency department and 13 from outpatient clinics.

The ALRI group and control groups were not significantly different with respect to sex (approximately 60% males and 40% females in both groups) and age at enrollment ( $13.4 \pm 13.8$  months and  $13.8 \pm 15.2$  months respectively). All but six participants identified their ethnicity as Caucasian or Aboriginal/Métis (Asian 3, Black 2, Other 1). The ethnicity categories were therefore collapsed into Caucasian and Non-Caucasian, and separate analyses considered the Caucasian and Aboriginal/Métis groups. ALRI subjects were significantly more likely to be Non-Caucasian (OR 3.5, 95% CI: 1.9, 6.4) compared to Caucasian. They were also more likely to have self-reported Aboriginal/Métis ancestry compared to Caucasian (OR 3.0, 95% CI: 1.7, 5.6).

Finally, ALRI subjects were significantly more likely to live in Northern Saskatchewan (OR 3.6, 95% CI 1.7, 7.5), to have a person-to-bedroom ratio greater than 1 (OR 2.1, 95% CI: 1.1, 3.7), to have a household smoking contact (OR 3.0, 95% CI 1.6, 5.4), and an incomplete immunization status (OR 1.9, 95% CI 1.0, 3.6). The presence of a heart condition, daycare attendance and breastfeeding were not significantly associated with ALRI (Table 3).

The mean vitamin D intake of control subjects was 60 IU/kg/d compared to 48 IU/kg/d in the ALRI group ( $P=0.09$ ). The standard deviation for vitamin D intake was 44 IU/kg/d. In order to determine if a certain level of vitamin D intake is associated with the risk of ALRI, vitamin D intake was dichotomized as greater and equal, or less than 40, 60, 80 or 100 IU/kg/d. Bivariate analysis was performed at each level (Table 4). A daily intake of less than 60 IU/kg/d was significantly associated with ALRI (OR 2.5, 95% CI: 1.3, 4.9) as was an intake of less than 80 IU/kg/d (OR 2.8, 95% CI: 1.3, 6.2).

In the multivariate model, a person-to-bedroom ratio greater than one (OR 1.8, 95% CI: 1.1, 5.3), a household smoking contact (OR 2.4, 95% CI: 1.0, 5.6) and vitamin D intake less than 80 IU/kg/d (OR 4.9, 95% CI: 1.5, 16.4) remained significantly associated with ALRI (Table 5). Substituting the Aboriginal/Métis variable with the collapsed ethnicity variable of Non-Caucasian did not significantly change the results of the multivariate analysis. When a vitamin D intake of less than 60 IU/kg/d was substituted into the model, only person-to-bedroom ratio (OR 2.3, 95% CI: 1.0, 4.9) and vitamin D intake were statistically significant (OR 2.7, 95% CI: 1.0, 7.3).

Finally, post-hoc analysis was performed examining the pneumonia and bronchiolitis groups separately. A vitamin D intake of less than 80 IU/kg/d was found to be significantly

associated with pneumonia (OR 7.9, 95% CI: 1.8, 35.5), but not bronchiolitis (OR 1.7, 95% CI: 0.7, 4.0).

## Discussion

The objective of this study was to determine if an association existed between vitamin D intake and ALRI in young children during the winter months when UVB radiation is low. In a group of children aged less than 5 years receiving hospital based care, those with ALRI had a lower vitamin D intake. This result approached statistical significance, but the analysis was underpowered due to a larger than expected standard deviation in the study population. However, bivariate analysis using different thresholds for vitamin D intake showed that intakes of less than 60 and 80 IU/kg/day were both significantly associated with ALRI.

Aboriginal ancestry, residence in northern Saskatchewan, lower socioeconomic status, exposure to household smoking, and incomplete immunizations were also associated with an increased risk of ALRI. As ethnicity and socio-economic status have previously been associated with vitamin D status, these factors were controlled for in the multivariate model (26-29). When controlling for these factors, a vitamin D intake of less than 80 IU/kg/d (2 mcg/kg/d) remained significant and was associated with a 4-fold increase in the risk of ALRI compared to children with an intake of greater than 80 IU/kg/d. Similarly, although not as statistically robust, the threshold level of 60 IU/kg/d remained associated with ALRI after controlling for other risk factors. These data suggest a threshold vitamin D intake, around 60 to 80 IU/kg/d, above which there might be some protection against ALRI.

In addition to its role in influencing bone health, vitamin D is also now known to have important effects on immune and inflammatory responses. Vitamin D modulates white blood cell proliferation, maturation and cytokine expression through cognate receptors on lymphocytes and macrophages (30-32). Vitamin D receptor signaling contributes to the expression of antimicrobial peptides and toll-like receptors, molecules important for innate defense against both viruses and bacteria (33,34). These mechanisms might at least partly explain why rickets, as well as subclinical vitamin D deficiency, is associated with ALRI in children from developing countries (10-14). Furthermore, in a randomized controlled trial, children aged 1-36 months with pneumonia who received a single oral dose of 100,000 IU of D3 were less likely to have a repeat episode in the 90 days after supplementation (35).

In North America, the link between ALRI and vitamin D has not been as clear. The authors' own study examining ALRI and



Table 3. Univariate analysis of demographic and ALRI risk factors.

Variable	Controls % (n=92)	ALRI % (n=105)	Odds Ratio (95% CI)	P value
<b>Gender</b>				
Male	57.8% (52)	59.2% (61)	1.1 (0.6, 1.9)	0.839
Female*	42.2% (38)	40.8% (42)		
<b>Age</b>				
Less than 2 months	33.3% (28)	22.0% (22)	0.7 (0.3, 1.4)	0.307
2 to 11 months	25.0% (21)	38.0% (38)	1.6 (0.8, 3.2)	0.198
12 to 60 months*	41.7% (35)	40.0% (40)		
<b>Medical history</b>				
Heart condition—yes	2.3% (2)	4.9% (5)	2.1 (0.4, 11.3)	0.370
Heart condition—no*	97.7% (84)	95.1% (98)		
<b>Socioeconomic status Person/Bedroom</b>				
Ratio > 1	51.8% (44)	68.9% (38)	2.1 (1.1, 3.7)	0.02
Ratio < 1*	48.2% (41)	31.1% (32)		
<b>Daycare</b>				
Attends	30.6% (26)	30.1% (32)	1.0 (0.5, 1.8)	0.942
Does not attend*	69.4% (59)	69.6% (71)		
<b>Region</b>				
Northern Saskatchewan	15.2% (12)	39.1% (36)	3.6 (1.7, 7.5)	0.001
Southern Saskatchewan*	84.8% (67)	60.9% (56)		
<b>Smoking contact</b>				
Household contact	34.9% (30)	61.4% (62)	3.0 (1.6, 5.4)	<0.0001
No household contact*	65.1% (56)	38.6% (39)		
<b>Prematurity</b>				
Less than 36 weeks	7.0% (6)	9.9% (10)	1.5 (0.5, 4.2)	0.478
Above 36 weeks*	93.0% (80)	90.1% (91)		
<b>Breastfeeding</b>				
Never, less than 6 mos	58.8% (50)	69.0% (69)	1.6 (0.9, 2.8)	0.151
Current, minimum 6 mos*	41.2% (35)	31.0% (31)		
<b>Immunization status</b>				
Up to date	73.3% (63)	58.8% (60)	1.9 (1.0, 3.6)	0.039
None/incomplete*	27.7% (23)	41.2% (42)		
<b>Ethnicity</b>				
Caucasian	66.7% (56)	39.6% (40)	3.0 (1.7, 5.6)	<0.0001
Aboriginal (First Nations/Métis)*	33.3% (28)	60.4% (61)		

\*Reference category for each dichotomous or ordinal grouping.

25(OH) vitamin D levels did not show a statistically significant association, but a trend was observed with the pneumonia patients having lower 25(OH)D levels compared to those with bronchiolitis (15). In addition, patients with severe disease were more likely to have lower serum concentrations of 25(OH)D.

Correlation between vitamin D intake and serum 25(OH)D levels was poor in our sample, possibly because patients had 25(OH)D collected at variable times during their illness, depending on when they were scheduled to have blood work. Serum 25(OH)D levels may have been impacted by medications, IV fluids and the illness



Table 4. Comparison of Vitamin D Intake among ALRI and control subjects.

Vitamin D Intake	Controls % (n=83)	ALRI % (n=97)	Odds Ratio (95% CI)	P value
Under 40 IU/kg/day	41.0 (34)	47.4 (46)	1.3 (0.7, 2.4)	0.385
Above 40 IU/kg/day	59.0 (49)	52.6 (51)		
Under 60 IU/kg/day	60.2 (50)	79.4 (77)	2.5 (1.3, 4.9)	0.006
Above 60 IU/kg/day	39.8 (33)	20.6 (20)		
Under 80 IU/kg/day	73.5 (61)	88.7 (86)	2.8 (1.3, 6.2)	0.011
Above 80 IU/kg/day	26.5 (22)	11.3 (11)		
Under 100 IU/kg/day	81.9 (68)	90.7 (88)	2.1 (0.9, 5.2)	0.089
Above 100 IU/kg/day	18.1 (15)	9.3 (9)		

Table 5. Multivariate model of risk factors\* for ALRI.

Risk factor	Odds Ratio	95% CI	P value
Male	1.2	0.6, 2.6	0.583
Age, less 2 months	1.3	0.4, 3.8	0.647
Age, 2 to 11 months	1.8	0.7, 4.5	0.192
Person to bedroom ratio > 1	1.8	1.1, 5.3	0.028
Northern Residence	2.1	0.8, 5.6	0.125
Household smoking contact	2.4	1.0, 5.6	0.045
Inadequate breastfeeding	0.7	0.3, 1.7	0.520
Incomplete immunization	0.9	0.4, 2.2	0.874
Vitamin D intake <80 IU/kg/day	4.9	1.5, 16.4	0.010
Aboriginal/Métis	1.8	0.7, 4.4	0.208

\*Odds ratios were calculated using the following dichotomous or ordinal grouping as the reference: female, 12 to 59 months of age, person to bedroom ratio  $\leq 1$ , residence in southern Saskatchewan, no household smoking contact, breastfed under 6 months, up to date immunizations, Vitamin D intake greater or equal 80 IU/kg/day, Caucasian.

itself (17,18). Vitamin D intake may be a reasonable alternative in estimating pre-illness vitamin D status. Interestingly, two recent publications measuring 25 hydroxyvitamin D in cord blood showed that infants with lower levels were more likely to develop respiratory tract infection during the first year of life (36,37).

Another Canadian study examining young children with bronchiolitis did not show lower vitamin D levels in this group, although they were found to have a specific vitamin D receptor (VDR) polymorphism resulting in an under active VDR (19,38). It has been suggested that this polymorphism may need higher levels of 25(OH)D, and thus higher vitamin D intake, to overcome the hypoactive VDR and provide protection against bronchiolitis. These findings might explain why in our subgroup analysis, a vitamin D intake of less than 80 IU/kg/d was associated with pneumonia but not bronchiolitis. The role of vitamin D in ALRI might not be limited to serum 25(OH)D

levels, and may instead be related to the level of intake, the study population (race and genetic make-up) and the disease process (bronchiolitis vs. pneumonia).

The Canadian Pediatric Society recommends that infants receive 400 IU/d of vitamin D in the first year of life (800 IU north of the 55th parallel), and the American Academy of Pediatrics recommends this amount for children of all ages (24,39). This level of supplementation should be sufficient to prevent vitamin D deficient rickets; however it may not be adequate to protect against other illnesses or achieve the recommended minimum serum 25(OH)D levels of 75-80 nmol/L (24,40). For example, in a recent Canadian study, more than 50% of infants aged less than 2 years had a serum 25(OH)D level less than 80 nmol/L despite having a vitamin D intake of 400 IU/d (41).

The results of the present study suggest that apart from young infants (<6 kg), 400 IU/d would be inadequate to achieve a





level of intake above 80 IU/kg/day, and that a more appropriate vitamin D dose might be better estimated according to weight. In fact, in their position statement, the Canadian Pediatric Society has suggested that infants and young children may need a vitamin D intake up to 2.5 mcg/kg/d (100 IU/kg/d) in order to optimize their serum 25(OH)D levels (24). Furthermore, a study correlating vitamin D intake and serum levels suggested that vitamin D supplementation in infants should consider their rapid body weight increment (42). Finally, the 2011 Institute of Medicine recommendations for vitamin D intake consider benefits for bone health only but do suggest different dosing based on age. In addition to recommended daily intakes of 400 and 600 IU for children under and over 1 year of age, the IOM provides an upper limit for vitamin D intake based on 6 different pediatric age ranges (43).

There are a number of limitations to the present study, the first of which relates to the inherent imprecision of dietary recall. In addition, a number of assumptions were made in calculating participants' vitamin D intake, including the milk intake of breastfed infants, and the vitamin D content of breastmilk, and of supplements if they were not named. Sun exposure was also not considered, although vitamin D synthesis through skin exposure during fall and winter months is negligible above latitudes greater than 40 degrees (41).

Further research is needed to better correlate vitamin D intake with serum 25(OH)D levels in children of different ages. Additional studies should further explore the relationship of vitamin D intake and 25(OH)D levels with various disease states. Specifically, the results of this study should be confirmed. Finally, consideration should be given to the idea that optimal daily dosing of vitamin D may be better described according to a child's weight.

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