



All Student Publications

2013-06-10

Vitamin D Deficiency and Acute Lower Respiratory Infections in Children Under 5 Years of Age: A Systematic Review

Allison Larkin

Follow this and additional works at: <https://scholarsarchive.byu.edu/studentpub>

 Part of the [Nursing Commons](#)

The College of Nursing showcases some of our best evidence based scholarly papers from graduate students in the Family Nurse Practitioner Program. The papers address relevant clinical problems for advance practice nurses and are based on the best evidence available. Using a systematic approach students critically analyze and synthesize the research studies to determine the strength of the evidence regarding the clinical problem. Based on the findings, recommendations are made for clinical practice. The papers are published in professional journals and presented at professional meetings.

BYU ScholarsArchive Citation

Larkin, Allison, "Vitamin D Deficiency and Acute Lower Respiratory Infections in Children Under 5 Years of Age: A Systematic Review" (2013). *All Student Publications*. 9.
<https://scholarsarchive.byu.edu/studentpub/9>

This Master's Project is brought to you for free and open access by BYU ScholarsArchive. It has been accepted for inclusion in All Student Publications by an authorized administrator of BYU ScholarsArchive. For more information, please contact scholarsarchive@byu.edu, ellen_amatangelo@byu.edu.

Vitamin D Deficiency and Acute Lower Respiratory Infections
in Children Under 5 Years of Age: A Systematic Review

Allison Joyce Holt Larkin

A literature review submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Master of Science

Jane Lassetter, Chair

College of Nursing

Brigham Young University

June 2013

Copyright © 2013 Allison Larkin

All Rights Reserved

ABSTRACT

Vitamin D Deficiency and Acute Lower Respiratory Infections

in Children Under 5 Years of Age: A Systematic Review

Allison Larkin
College of Nursing, BYU
Master of Science

Introduction: Acute lower respiratory infection (ALRI) is the leading cause of mortality in children 5 years and younger. The purposes of this literature review were to examine vitamin D deficiency (VDD) and ALRI in children 5 years and younger and make recommendations regarding vitamin D to prevent ALRI.

Method: Databases were searched for studies investigating VDD and ALRI in children 5 years and younger. Two independent reviewers assessed internal validity using the U.S. Preventive Services Task Force grading criteria.

Results: Eighteen studies met inclusion criteria. VDD was associated with increased risk or increased severity of ALRI in 13 studies, but 4 studies did not find significant associations. One study found high maternal vitamin D was associated with ALRI in infants.

Discussion: Research suggests VDD puts children at risk for ALRI. Vitamin D supplementation is a low-cost, low-risk intervention providers should consider for children, especially those at high risk for ALRI.

Keywords: Vitamin D, acute lower respiratory infection, pneumonia, bronchiolitis

ACKNOWLEDGEMENTS

My appreciation goes to Jane Lassetter, my committee chair, for her constant guidance, encouragement, and patience. Her skills at writing effectively and concisely were priceless to this project. I also thank my sweet husband who constantly supported me while completing my Master of Science and this scholarly paper.

TABLE OF CONTENTS

TITLE PAGE	i
ABSTRACT	ii
ACKNOWLEDGEMENTS	iii
TABLE OF CONTENTS	iv
INTRODUCTION	1
REFERENCES	20

Vitamin D Deficiency and Acute Lower Respiratory Infections in Children Under 5 Years of Age: A Systematic Review

In 1903 Niels Ryberg Finsen, a Danish doctor, received the Nobel Prize for discovering a novel and effective treatment for skin tuberculosis: light. Finsen cured patients with lupus vulgaris through phototherapy (Nobel Foundation, 1903), and by the 1920s, sun exposure was becoming an increasingly popular treatment for tuberculosis (Roelandts, 2002). The efficacy of phototherapy might lie in the fact that sunlight increases vitamin D levels. Eventually, with the discovery of antibiotics, light intervention was forgotten. However, more than a century later, the possibilities of vitamin D as treatment for and an aid in prevention of respiratory illnesses are now being discovered (Manaseki-Holland et al., 2010; Camargo et al., 2012).

A possible connection between vitamin D deficiency (VDD) and respiratory infections has been found. As early as 1975, Salimpour (1975) studied 200 rachitic children (rickets is caused by VDD and calcium deficiency), ages 0 to 14 years, in Tehran, Iran and found 43% also suffered from pneumonia. Research also has associated VDD with acute lower respiratory tract infection (ALRI), which includes bronchiolitis and pneumonia (Karatekin, Kaya, Salihoğlu, Balci, & Nuhoglu, 2009; Roth, Shah, Black, & Baqui, 2010). This association is important because ALRI is the most common cause of global child mortality, annually accounting for the deaths of 2 million children less than 5 years of age (Bryce, Boschi-Pinto, Shibuya, & Black, 2005). In the U.S., hospitalizations for respiratory syncytial virus (RSV) infections, a common cause of bronchiolitis, cost \$500 million per year, and a co-infection with pneumonia doubles the cost of a hospitalization (Pelletier, Mansbach, & Camargo, 2006). If vitamin D could prevent or treat respiratory infections in children, it could save lives and decrease healthcare costs.

Current treatment of ALRI is mostly supportive. Nasopharyngeal suctioning, oxygen therapy, and antipyretics might be used. Antibiotics are sometimes administered if the infection is thought to be bacterial rather than viral (Kabra, Lodha, & Pandey, 2010).

Prevention of ALRI is limited primarily to hand washing and minimizing exposure to bacteria and viruses that cause respiratory infections. Although Palivizumab (Synagis) is a vaccine that has been shown to be effective in preventing RSV (IMpact-RSV Study Group, 1998; Winterstein, Hampp, & Saidi, 2012), it is costly and limited by the Federal Drug Administration to high-risk infants. Typically, high-risk infants receive Palivizumab once a month from November to April. Palivizumab costs on average \$1074 per 50 mg vial and is dosed at 15 mg per kg (Mahadevia, Masaquel, Polak, & Weiner, 2012), making the treatment cost for a 3 kg infant approximately \$966 for a single dose of Palivizumab, or approximately \$6000 for six months' administration. Thus, new effective ways to prevent and treat ALRI would be beneficial.

Therefore, the purposes of this systematic review are threefold: (a) to conduct a thorough review of literature for studies regarding the association between VDD and ALRI in children 5 years of age or younger, (b) to critically appraise these articles using the United States Preventive Services Task Force (USPSTF) rating system (Harris et al., 2001), and (c) to make recommendations for nurse practitioners regarding the use of vitamin D to prevent ALRI in this age group.

Background

Vitamin D is an essential steroid hormone. It is produced in the skin through solar ultraviolet B radiation converting 7-dehydrocholesterol to pre-vitamin D₃, which is then converted to vitamin D₃ in the liver (DeLuca, 2004). Vitamin D is primarily synthesized from

sun exposure, but can also be obtained through dietary intake or supplements of vitamin D2 or vitamin D3 (Holick, 2007).

Both the lower and upper limits of healthy serum vitamin D are unclear. The Institute of Medicine (2011) defines VDD as serum level less than 20 nanograms per milliliter, but in research studies the threshold for VDD varies widely. Researchers have questioned whether current recommendations of vitamin D intake are sufficient for optimal health outcomes (Bischoff-Ferrari, Giovannucci, Willett, Dietrich, & Dawson-Hughes, 2006; Mansbach, Ginde, & Camargo, 2009). An estimated 1 billion people worldwide have vitamin D insufficiency (21-29 ng/mL) or deficiency (Holick, 2007). Recently, Dror et al.'s (2013) study identified vitamin D levels in the 20-36 ng/mL range with the lowest risk for morbidity and mortality for adults over 45 years of age.

Although vitamin D is fairly simple to obtain, cultural and health practices might lead to vitamin D insufficiency or VDD by preventing infants from acquiring vitamin D from sun exposure. First, in some countries infants are swaddled when outdoors, minimizing their skin exposure to the sun. Second, even when exposed to the sun, mothers in many cultures protect their infants and children with sunscreen to prevent sunburns and skin cancer. Sunscreen suppresses vitamin D3 synthesis by blocking the absorption of UV-B radiation (Matsuoka, Ide, Wortsman, MacLaughlin, & Holick, 1987). Third, mothers are likely to have vitamin D insufficiency or VDD for the same reasons as their infants. When mothers do not have sufficient levels of vitamin D, their breast milk will be low in vitamin D. Cultural practices like these contribute to low vitamin D levels.

Because vitamin D is primarily synthesized through sun exposure, VDD appears to follow a seasonal pattern of higher vitamin D levels during summer and lower levels in winter.

Interestingly, researchers have found associations between VDD and seasonal respiratory illnesses, such as upper respiratory infections (Ginde, Mansbach, & Camargo, 2009). Grant (2008) similarly hypothesized that sun exposure and its effect on vitamin D levels could help explain the seasonality of childhood respiratory infections. These infections, such as bronchiolitis or pneumonia, peak in the winter when sunlight is scarce and dissipate in the summer.

Not only are vitamin D levels associated with childhood respiratory infections, they also might affect lung growth and maturation even before birth. Vitamin D receptors are prevalent in rat fetal lung tissue during lung cell differentiation and the start of surfactant production (Nguyen et al., 2004). In addition, Rehan et al. (2002) found 25-hydroxyvitamin D (25[OH]D), the serum metabolite measured to determine vitamin D status, actually stimulates synthesis of surfactant in alveolar type II cells of rat fetal lungs. Surfactant is essential to preventing infant respiratory distress syndrome by avoiding the collapse of alveoli. Therefore, vitamin D might promote prenatal lung development by facilitating surfactant production.

Method

Identification of Studies

An electronic search was conducted to identify studies from 2004–2013 in the following databases: Medline, CINAHL, and Cochrane Library. The search terms used were vitamin D, 25-hydroxyvitamin D, child, maternal, infant, respiratory, infection, and pneumonia. References from relevant articles were reviewed for applicable studies. Only English articles evaluating the relationship between vitamin D and ALRI in children 0 to 5 years of age were included. Studies were excluded if they included adults or children over 5 years of age or focused on asthma. We included one classical study published prior to 2004 (Muhe & Lulseged, 1997). A total of 18

articles met the criteria for the review, including 6 cohort studies, 8 case-control studies, 1 retrospective case study, 1 cross-sectional study, and 2 randomized control trials.

Conversion of Measurement and VDD Definitions

Two different units of measurement were used in the reviewed studies to assess vitamin D levels: nanomol per liter (nmol/L) and nanogram per milliliter (ng/ml). We converted all values to ng/mL to facilitate comparison between studies. For converting vitamin D levels, 1 nmol/L equals 0.4 ng/ml (National Institutes of Health, 2011). Therefore, values in nmol/L were multiplied by 0.4 to convert to ng/mL.

The thresholds for determining VDD vary widely, from 9-20 ng/mL. This variation makes it difficult to compare findings of the studies. The levels, where available, were converted if necessary to ng/mL.

Assessment of Internal Validity

The two authors independently assessed the studies' internal validity using the USPSTF criteria (Harris et al., 2001). This includes criteria for evaluating five different types of studies: systematic reviews, case-control studies, randomized controlled trials (RCTs), cohort studies, and diagnostic accuracy studies (see Table 1). Each study is given a rating of good, fair, or poor based on the criteria for that type of study.

Table 1.

U.S. Preventive Services Task Force Criteria for Grading Internal Validity

Study Design	Criteria
Systematic review	Comprehensiveness of sources/search strategy used Standard appraisal of included studies

	Validity of conclusions
	Recency and relevance
Case-control studies	Accurate ascertainment of cases
	Nonbiased selection of cases/controls with exclusion criteria applied equally to both
	Response rate
	Diagnostic testing procedures applied equally to each group
	Appropriate attention to potential confounding variables
Randomized control trials and cohort studies	Initial assembly of comparable groups
	For RCTs: adequate randomization, including concealment and whether potential confounders were distributed equally among groups
	For cohort studies: consideration of potential confounders with either restriction
	or measurement for adjustment in the analysis; consideration of inception cohorts
	Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
	Important differential loss to follow-up or overall high loss to follow-up
	Measurements: equal, reliable and valid (includes masking of outcome assessment)
	Clear definition of interventions
	All important outcomes considered
	Analysis: adjustment for potential confounders for cohort studies, or intention to treat analysis for RCTs
Diagnostic accuracy studies	Screening test relevant, available for primary care, adequately described

Study uses a credible reference standard, performed regardless of test results

Reference standard interpreted independently of screening test

Handles indeterminate results in a reasonable manner

Spectrum of patients included in study

Sample size

Administration of reliable screening test

Harris et al. (2001). Permission to republish received from Elsevier.

Results

Internal Validity of Studies

According to assessment using the USPSTF criteria, the authors rated each of the studies' internal validity as fair. Weaknesses that prevented the studies from obtaining a "good" rating included high loss to follow up, failure to consider all important outcomes, or failure to adjust for potential confounding variables. According to the authors' assessment, none of the studies had a fatal flaw, which is required for a "poor" rating.

Rickets and ALRI

Two research groups found significant associations between rickets, which is caused by VDD and calcium deficiency, and ALRI. In both studies rickets was identified by clinical signs and confirmed by wrist x-ray. First, in a matched case-control study in the Ethio-Swedish Children's Hospital in Ethiopia involving 500 children less than 5 years of age admitted with pneumonia and 500 controls with no evidence of pneumonia, rickets was significantly more prevalent among children with pneumonia than among the controls (Muhe & Lulseged, 1997; 210 vs. 20, matched odds ratio 22.11, $p < 0.0001$). However, these researchers did not find an increase in mortality of children with pneumonia and rickets compared to those with only

pneumonia (RR 1.16, $p = 0.20$). Second and similarly, Najada, Habashneh, and Khader (2004) conducted a study involving 443 infants aged 0 to 24 months in Amman, Jordan and found significantly more rachitic infants were admitted with lower respiratory tract diseases than non-rachitic controls (85% vs. 30%, $p < 0.01$). The length of hospital stay was significantly longer for rachitic infants than non-rachitic infants (9.5 days vs. 7.4, $p = 0.002$).

In Muhe and Lulseged's (1997) study, the case and control groups differed significantly in family size, birth order, number of people living in their homes, and months of exclusive breastfeeding. However, even after controlling for these variables, the incidence of rickets among children with pneumonia was still 13 times higher than among controls (13.37, $p < 0.001$). The rachitic and non-rachitic children in Najada et al.'s (2004) study also differed significantly in the birth order of child, family size, mode of feeding, outdoor dressing of mothers (covering body with thick, dark clothing), and presence of anemia; however, Najada et al. did not state whether they controlled for these variables in their analysis.

Correlation Between Vitamin D Level and ALRI

Research has also been conducted regarding correlation between infant vitamin D levels and ALRI. Two studies found 25(OH)D levels were significantly lower in infants with ALRI than in controls (Karatekin et al., 2009; Roth et al., 2010). Karatekin et al. (2009) studied 25 newborns with ALRI and 15 healthy newborn controls in Istanbul, Turkey and found newborns with ALRI had significantly lower serum 25(OH)D concentrations than control newborns (9.12 ± 8.88 ng/ml vs. 16.33 ± 13.42 ng/ml, $p = 0.011$). Roth et al. (2010) had similar results when comparing 25 case-control pairs in Sylhet, Bangladesh. The cases, children 1–18 months hospitalized with ALRI, were matched to controls based on age, sex, and village. In their study, the mean serum 25(OH)D of cases was significantly lower than controls (11.6 vs. 15.6 ng/mL, p

= 0.015). In another case-control study in India, Wayse, Yousafzai, Mogale, and Filteau (2004) found serum 25(OH)D > 9 ng/mL was associated with a significantly lower risk of severe ALRI (OR: 0.09; 95% CI [0.03–0.24]; $p < 0.001$).

Three studies also found an association between infant ALRI and cord blood or maternal vitamin D levels. In a prospective birth cohort study of 156 infants in the Netherlands, Belderbos et al. (2011) found low cord blood vitamin D increased the risk of RSV. Infants with cord blood 25(OH)D < 20 ng/mL had an adjusted relative risk of 6.2 compared to infants with 25(OH)D \geq 30 ng/mL (95% CI [1.6–24.9], $p = 0.01$). Camargo et al. (2011) conducted a similar study in New Zealand and found newborns with cord blood 25(OH)D levels < 10 ng/mL were twice as likely to develop respiratory infections at 3 months of age compared with 3-month-old infants who had 25(OH)D \geq 30 ng/mL (aOR = 2.04) cord blood levels as newborns. Likewise, Morales et al. (2012) studied 1693 children under 5 years of age in Spain and found higher maternal vitamin D levels during pregnancy were associated with a decreased risk of ALRI in the infants' first year of life (Quartile 4 vs. Quartile 1, odds ratio = 0.67, 95% CI [0.50–0.90], $p = 0.016$).

Not all researchers found a decrease in ALRI with increased vitamin D levels. Camargo et al. (2007) conducted research in Massachusetts and did not find an association between mothers' intake of vitamin D and their infants' risk of respiratory infection ($p = 0.09$). In a study done in Alberta, Canada, Roth, Jones, Prosser, Robinson, and Vohra (2009) did not find a significant difference in VDD between 64 cases of ALRI and 65 controls without a history of hospitalization for ALRI, using either the 25(OH)D threshold of < 16 ng/mL (4.7 vs. 1.5%, $p = 0.365$) or < 32 ng/mL (51.6 vs. 56.9%, $p = 0.598$). McNally et al. (2009) similarly found no difference in mean vitamin D levels between 105 cases of ALRI and 92 controls in Saskatchewan, Canada (32.4 ± 15.6 vs. 33.2 ± 12.0 ng/mL, $p = 0.71$). However, the difference

in prevalence of 25(OH)D levels < 20 ng/mL between the pneumonia subgroup and controls was approaching significance (30% vs. 16%, $p = 0.07$). In a secondary analysis of the same data, Leis et al. (2012) found children with a vitamin D intake of less than 80 IU/kg/d were more than four 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]).

Severity of ALRI

Some researchers investigated vitamin D's role in the severity of ALRI in children. In a study of 152 children less than 59 months of age with pneumonia at Al-Sabeen hospital in Sana'a, Yemen, VDD was an independent predictor of persistent hypoxemia for children admitted with pneumonia (Banajeh, 2009; $p = 0.021$). Rachitic children were four times more likely than non-rachitic children to fail treatment 30 days after enrollment in the study (20.6 vs. 6%, 4.1; [95% CI (1.2–14.4). $p = 0.029$]). Treatment failure was defined as modification of treatment because of worsening clinical condition, development of comorbid condition such as bacterial meningitis, or death. Likewise, Inamo et al. (2011) studied 28 infants in Tokyo, Japan and found compared to infants with 25(OH)D of 6 ng/mL or more, infants with 25(OH)D < 4 ng/mL were significantly more likely to need supplementary oxygen and ventilator management ($p < 0.01$). Similarly, McNally et al. (2009) found vitamin D levels of infants with ALRI in a Canadian PICU were significantly lower than controls who were hospitalized for something other than ALRI (19.6 ± 9.6 vs. 33.2 ± 12.0 ng/mL, $p = 0.001$). These studies suggest VDD might increase the severity of a respiratory infection, and infants and children with VDD and ALRI might require higher levels of care than children with sufficient vitamin D levels.

Other researchers did not find a difference in severity of ALRI and vitamin D levels. In a double-blind RCT in inner-city Kabul, Afghanistan comparing oral vitamin D supplementation

to placebo in 224 children with pneumonia, there was no difference in mean days to recovery between the group who received vitamin D supplements and the group who received placebos (4.74 vs. 4.98 days, $p = 0.17$; Manaseki-Holland et al., 2010). Additionally, Carroll et al. (2011) did a cross-sectional study of 252 mother-infant dyads in Tennessee and compared the mothers' vitamin D level with their infants' bronchiolitis score, which is a tool used to assess severity of respiratory symptoms. In propensity score-adjusted sensitivity models, Carroll et al. did not find a significant association between the maternal 25(OH)D level and the infants' bronchiolitis score (aOR, 0.76, 95% CI [0.52–1.11]).

Findings from one study contradict research indicating potential benefits of vitamin D to help prevent or treat ALRI in young children. In a study in Southampton, United Kingdom, Gale et al. (2008) found high maternal 25(OH)D levels were associated with increased incidence of ALRI in infants. Compared to mothers in late pregnancy who were in the bottom quarter of 25(OH)D levels, mothers in the top quarter of 25(OH)D levels were significantly more likely to report a diagnosis of pneumonia or bronchiolitis in their infants (OR 4.80, 95% CI [1.01 – 22.73]). No significant associations between maternal 25(OH)D concentration and risk of reported bronchitis or chest infections or overall respiratory infections were found (Gale et al., 2008).

Effects on Immune System

Two research groups investigated the effect of vitamin D on the immune system during ALRI. In a study in Sana'a, Yemen, Banajeh (2009) found VDD significantly decreased the percentage of circulating polymorph nuclear neutrophils (37 vs. 47%, adjusted OR 0.71 [95% CI (0.53–0.95)], $p = 0.02$), which are important innate immune cells that migrate into the lung tissues and kill bacteria and viruses through phagocytosis. During the RCT in Afghanistan by

Manaseki-Holland et al. (2010), 224 children admitted with pneumonia were randomly assigned to receive either a single-dose 100,000 IU oral vitamin D supplement or a placebo. No vitamin D levels were assessed during the trial, and it was not stated when the supplements or placebos were administered. Manaseki-Holland et al. (2010) assessed the frequency of repeat pneumonia episodes during the 90-day post-treatment period. Children who received a vitamin D supplement had a significantly lower risk of a repeat episode compared to children who received a placebo (92 vs. 122, RR 0.78 [95% CI (0.64–0.94)], $p = 0.01$). These results suggest VDD weakens the immune system, and supplementation might be beneficial.

In Manaseki-Holland and associates' (2012) double-blind RCT in Afghanistan, 3,046 infants aged 1 to 11 months were randomly assigned to oral administration of either vitamin D3 100,000 IU or a placebo every 3 months for 18 months. They did not find a significant difference in incidence of first or only pneumonia between the placebo group (0.137, 0.121–0.155) and the vitamin D group (0.145 per child per year, 95% CI [0.129–0.164]).

During three studies, vitamin D supplements were administered. Supplements given were 100,000 IU orally once (Manaseki-Holland et al., 2010), 100,000 IU orally every 3 months for 18 months (Manaseki-Holland et al., 2012), and 600,000 IU via intramuscular injection once (Najada et al., 2004). Parents did not report any adverse reactions to or side effects from vitamin D supplements administered to their children.

Discussion

Limitations of Studies

Units of measurement. Comparing the study results was difficult because studies varied in unit of measurement and definition of VDD. Some articles did not even define VDD. When

defined, either nanogram per milliliter (ng/ml) or nanomol per liter (nmol/L) was the unit of measurement. We converted vitamin D values to ng/mL to facilitate comparison between studies.

In addition to two different units of vitamin D measurement, researchers used different thresholds to determine VDD (see Table 2), with thresholds ranging from 9 to 20 ng/mL. This wide range could explain why some studies found VDD was significantly associated with ALRI in children whereas others did not. When using a higher threshold, researchers would be less likely to detect a difference in prevalence of VDD between cases with ALRI and controls.

Table 2.

Definitions of Vitamin D sufficiency (VDS), Insufficiency (VDI), and Deficiency (VDD) by 25(OH)D Level in Nanograms per Milliliter

Author	Definition of VDS	Definition of VDI	Definition of VDD
Banajeh (2009)			< 12
Belderbos et al. (2011)	No explicit definitions but four comparison groups used: < 10, < 20, 20 – 29.6, and ≥ 30		
Camargo et al. (2011)	No explicit definitions but categorized into three groups: < 9.9, 10 – 29.9, and ≥ 30		
Carroll et al. (2011)	> 12	8 – 12	< 8

Gale et al. (2008)	No explicit definitions but four groups compared: < 12, 12 – 20, 20 – 30, > 30	
Inamo et al. (2011)		≤ 15 Severe VDD: ≤ 5
Karatekin et al. (2009)		Two cut-offs used: < 10 (suggested by testing kit manufacturer) and < 20 (consensus of scientific understanding)
Leis et al. (2012)	30 – 32	
Manaseki-Holland et al. (2010)	< 20 considered “suboptimal”	< 12 associated with Rickets
McNally et al. (2009)	< 30	< 20
Morales et al. (2012)	< 30	
Roth, Jones, Prosser, Robinson, & Vohra (2009)	< 16	< 10
Wayse, Yousafzai, Mogale, & Filteau (2004)		< 9

Note: 25-hydroxyvitamin D (25[OH]D) is a biomarker of vitamin D status in circulation (Roth et al., 2010, p. 289)

Weaknesses in assessment. Different results might also be explained by lack of rigor in assessment tools. Gale et al. (2008) and Camargo et al. (2007) used maternal recall to determine if the mother's infant had ever been diagnosed with respiratory infections such as pneumonia, bronchiolitis, croup, or bronchitis. Camargo et al. (2007) further relied on maternal recall by asking mothers to complete a food frequency questionnaire and then using the information to assess vitamin D intake. Maternal self-report can be inaccurate because mothers might incorrectly remember past events or not understand the questions. Also, mothers might hesitate to report their children's illnesses if they believe illnesses would reflect poorly on their abilities as mothers.

Bronchiolitis scores were used exclusively to assess illness severity in Carroll et al.'s (2011) study, and individual scores were based on respiratory symptoms at one point in time. Trends in bronchiolitis scores are helpful in determining illness trajectory and effectiveness of respiratory treatments. However, these researchers apparently used a single bronchiolitis score for each child, which does not accurately reflect the extent or severity of illness over time. Additionally, Carroll et al. did not specify when the bronchiolitis score was determined, and scores can vary widely based on factors, such as whether symptoms were assessed and scored on admission versus prior to discharge, or whether the infant had recently been suctioned or received a respiratory treatment. These data collection methods have weaknesses that could affect the studies' results.

Control group. Researchers of the case-control studies differed on the criteria used for control participants. Some researchers recruited controls who were healthy children with no history of ALRI coming to a clinic for immunizations (Karatekin et al., 2009) or receiving elective surgery at the hospital (Roth et al., 2009). Roth et al. (2010) used population-based

sampling to find controls with no history of ALRI from the same villages as the cases in their study. In contrast, other researchers used controls who were children admitted to the hospital for illnesses other than ALRI (McNally et al., 2009; Muhe & Lulseged, 1997). Because of the effect vitamin D has on the immune system, children in this control group could have had low vitamin D levels as well. The various sampling methods used to determine control groups make it challenging to compare studies and generalize to the population of interest.

Season of study. The season during data collection might also limit generalizability of the studies. Belderbos et al. (2011) found 25(OH)D concentrations had a seasonal distribution with maximum in July and nadir, or lowest point, in January. They found a positive correlation between cord blood 25(OH)D level and monthly sun hours according to data from the Royal Netherlands Meteorological Institute ($r = 0.196$, $p = .01$). Differing seasons could also explain differences in the researchers' findings. For example, four studies were conducted during winter months (Carroll et al., 2011; Karatekin et al., 2009; Roth et al., 2009; Roth et al., 2010). During the winter, participants' vitamin D levels were likely affected by the lack of sunlight. This could be a confounding factor that was not considered in some studies.

Bacterial versus viral cause. Another factor potentially affecting the studies' results is whether the ALRI was caused by a bacteria or virus. Roth et al. (2009) found no difference between cases and controls in prevalence of vitamin D insufficiency in Canada. In contrast, Wayse et al. (2004) found adequate serum vitamin D to be associated with a lower the risk of ALRI in India. Roth et al. (2009) suggest the difference in findings between their study and the Wayse et al. (2004) study might be due to the causative agent. Bacterial pneumonia is common in developing countries like India, whereas the Roth et al. (2009) study in Canada included

mostly patients with viral ALRI. Vitamin D might have a different effect on bacterial versus viral ALRI.

Implications for Practice

Research indicates there might be an association between low vitamin D and ALRI in children under 5 years old. Maintaining both maternal vitamin D levels during pregnancy and an infant's own vitamin D levels might be protective against ALRI. Although further research is needed, nurse practitioners should consider assessing vitamin D levels and prescribing supplementation, especially for pregnant women and infants at high-risk for ALRI, such as infants born prematurely or with chronic lung disease.

Practitioners should consider the cost of vitamin D supplementation. It is a relatively inexpensive prophylaxis method that could be used in addition to Palivizumab for high-risk infants and independently for infants and children in general. Additionally, if vitamin D supplements help prevent ALRI or decrease severity, it saves expenses associated with treatment or hospitalization.

Practitioners should also consider side effects when supplementing with vitamin D. The three research groups that provided vitamin D supplementation reported no adverse events in their studies (Manaseki-Holland et al., 2010; Manaseki-Holland et al., 2012; Najada et al., 2004). Vitamin D is generally well tolerated, but toxicity causes hypercalcemia. The symptoms of hypercalcemia include constipation, anorexia, nausea, and vomiting initially, and then polyuria, nocturia, and polydipsia after renal impairment (Lewis, 2009). Symptoms of toxicity can be avoided if 25(OH)D levels are monitored and vitamin D dosage adjusted accordingly. Patients with normal kidney function are not likely to reach toxic levels because they are able to clear

excess vitamin D. Practitioners should be aware of these potential toxicity symptoms and watch for them in their patients.

Practitioners should consider vitamin D supplementation for women during pregnancy and lactation. The current recommendation of a multivitamin containing 400 IU of vitamin D might not be sufficient. In one study of healthy women, the majority were taking a daily prenatal vitamin, but 50% of the women and 65% of their newborns were vitamin D deficient (25[OH]D < 12 ng/mL) at birth (Lee et al., 2007). In addition, in a study of high-dose vitamin D supplements in lactating women, Hollis and Wagner (2004) found a maternal intake of 4000 IU/day was required to provide adequate vitamin D for both mothers and their breastfed infants. These findings suggest an implication for policy, which would be to increase the recommended amount of vitamin D in prenatal vitamins.

Infants can also benefit from vitamin D supplementation. Practitioners working in pediatrics could check 25(OH)D levels of infants during well-child checks, especially for infants with risk factors for ALRI, such as prematurity, immuno-deficiency, and chronic lung disease. Currently, the American Academy of Pediatrics recommends supplementing 400 IU per day of vitamin D for all breastfed infants (Wagner & Greer, 2008). Parents can administer vitamin D drops for supplementation in their children.

Vitamin D Fortification

Another implication of these findings is the need for food fortification with vitamin D in developing countries. The prevalence of rickets in some of the studies indicates the severe need for vitamin D. Natural food sources of vitamin D—mushrooms, alfalfa, and fatty fish—are not typically included in the infant diet. However, infants are likely to eat fortified dairy products and cereals. Fortification could aid in preventing both rickets and ALRI.

Implications for Research

Further research is needed on this subject. Most of the studies on ALRI and vitamin D levels have been case-control or birth cohort studies. It appears giving vitamin D to mothers and infants might be beneficial, but only two RCTs have been done investigating vitamin D supplementation as an intervention (Manaseki-Holland et al., 2010; Manaseki-Holland et al., 2012). Future RCTs should investigate the use of a daily vitamin D supplement, involve healthy infants or pregnant women as subjects, and follow up longitudinally. Additionally, RCTs should specify when the supplementation is given and report any side effects of vitamin D supplementation.

Conclusion

This systematic review revealed conflicting results. Among these studies, VDD was prevalent among both mothers and infants. Several of the studies found VDD to be associated with increased risk for ALRI; however, a handful did not. More research is needed to determine the role vitamin D plays in the development of ALRI and the effect supplementation can have. Vitamin D supplementation is inexpensive and low-risk; therefore, practitioners should recommend it for infants and children with good kidney function to help prevent ALRI.

References

- Banajeh, S. M. (2009). Nutritional rickets and vitamin D deficiency—Association with the outcomes of childhood very severe pneumonia: A prospective cohort study. *Pediatric Pulmonology, 44*, 1207-1215.
- Belderbos, M. E., Houben, M. L., Wilbrink, B., Lentjes, E., Bloemen, E. M., Kimpen, J. L. L, . . . Bont, L. (2011). Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. *Pediatrics, 127*(6), e1513-e1520.
- Bischoff-Ferrari, H. A., Giocannucci, E., Willett, W. C., Dietrich, T., & Dawson-Hughes, B. (2006). Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *American Journal of Clinical Nutrition, 84*(1), 18-28.
- Bryce, J., Boschi-Pinto, C., Shibuya, K., & Black, R. E. (2005). WHO estimates of the causes of death in children. *Lancet, 365*(9465), 1147-52.
- Camargo, C. A., Ganmaa, D., Frazier, L. A., Kirchberg, F. F., Stuart, J. J., Kleinman, K., . . . Rich-Edwards, J. W. (2012). Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. *Pediatrics, 130*(3), e561-e567.
- Camargo, C. A., Ingham, T., Wickens, K., Thadhani, R., Silvers, K. M., Epton, M. J., . . . Crane, J. (2011). Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics, 127*(1), e180-e187.
- Camargo, C. A., Rifas-Shiman, S. L., Litonjua, A. A., Rich-Edwards, J. W., Weiss, S. T., Gold, D. R., . . . Gillman, M. W. (2007). Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 years of age. *American Journal of Clinical Nutrition, 85*, 788-795.

- Carroll, K. N., Gebretsadik, T., Larkin, E. K., Dupont, W. D., Liu, Z., Van Driest, S., & Hartert, T. V. (2011). Relationship of maternal vitamin D level with maternal and infant respiratory disease. *American Journal of Obstetrics and Gynecology*, 205(3), 215.e1-215.e7.
- DeLuca, H. F. (2004). Overview of general physiologic features and functions of vitamin D. *American Journal of Clinical Nutrition*, 80(6), 1689-1696.
- Dror, Y., Giveon, S., Hoshen, M., Feldhamer, I., Balicer, R., & Feldman, B. (2013). Vitamin D levels for preventing acute coronary syndrome and mortality: Evidence of a non-linear association. *Journal of Clinical Endocrinology & Metabolism*, 98(5), 2160-2167.
- Gale, C. R., Robinson, S. M., Harvey, N. C., Javaid, M. K., Jiang, B., Martyn, C. N., . . . Cooper, C. (2008). Maternal vitamin D status during pregnancy and child outcomes. *European Journal of Clinical Nutrition*, 62, 68-77.
- Ginde, A. A., Mansbach, J. M., & Camargo, C. A. (2009). Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Archives of Internal Medicine*, 169(4), 384-390.
- Grant, W. B. (2008). Variations in vitamin D production could possibly explain the seasonality of childhood respiratory infections in Hawaii. *The Pediatric Infectious Disease Journal*, 27(9), 853.
- Harris, R. P., Helfrand, M., Woolf, S. H., Lohr, K. N., Mulrow, C. D., Teutsch, S. M., & Atkins, D. (2001). Current methods of the U.S. Preventive Services Task Force. *American Journal of Preventive Medicine*, 20(3S), 21-35.
- Holick, M. F. (2007). Vitamin D deficiency. *The New England Journal of Medicine*, 357, 266-281.

- Hollis, B. W. & Wagner, C. L. (2004). Vitamin D requirements during lactation: High-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *American Journal of Clinical Nutrition*, 80(6 suppl), 1752S-8S.
- Impact-RSV Study Group. (1998). Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics*, 102(3), 531-537.
- Institute of Medicine. (2011). *Dietary reference intakes for calcium and vitamin D*. Washington, DC: National Academies Press.
- Kabra, S. K., Lodha, R., & Pandey, R. M. (2010). Antibiotics for community acquired pneumonia in children. *Cochrane Database Systematic Reviews*, 2010(3), Art. No.: CD004874.
- Karatekin, G., Kaya, A., Salihoğlu, O., Balci, H., & Nuhoğlu, A. (2009). Association of subclinical vitamin D deficiency in newborns with acute lower respiratory infection and their mothers. *European Journal of Clinical Nutrition*, 63(4), 473-477.
- Lee, J. M., Smith, J. R., Philipp, B. L., Chen, T. C., Mathieu, J., & Holick, M. F. (2007). Vitamin D deficiency in a health group of mothers and newborn infants. *Clinical Pediatrics*, 46, 42-44.
- Leis, K. S., McNally, J., Montgomery, M. R., Sankaran, K., Karunanayake, C., & Rosenberg, A. M. (2012). Vitamin D intake in young children with acute lower respiratory infection. *Translational Pediatrics*, 1(1), 6-14.
- Lewis, J. L. (2009). Disorders of calcium concentration. *Merck Manual Online*. Retrieved from http://www.merckmanuals.com/professional/endocrine_and_metabolic_disorders/electrolyte_disorders/disorders_of_calcium_concentration.html#v1150427

- Manaseki-Holland, S., Maroof, Z., Bruce, J., Mughal, M. Z., Masher, M. I., Bhutta, Z. A., . . . Chandramohan, D. (2012). Effect on the incidence of pneumonia of vitamin D supplementation by quarterly bolus dose to infants in Kabul: A randomised controlled superiority trial. *Lancet*, *379*(9824):1419-27.
- Manaseki-Holland, S., Qader, G., Masher, M. I., Bruce, J., Mughal, M. Z., Chandramohan, D., & Walraven, G. (2010). Effects of vitamin D supplementation to children diagnosed with pneumonia in Kabul: A randomised controlled trial. *Tropical Medicine & International Health*, *15*(10), 1148-1155.
- Mansbach, J. M., Ginde, A. A., & Camargo, C. A. (2009). Serum 25-hydroxyvitamin D levels among US children aged 1 to 11 years: Do children need more vitamin D? *Pediatrics*, *124*, 1404-1410.
- Matsuoka, L. Y., Ide, L., Wortsman, J., MacLaughlin, J. A., & Holick, M. F. (1987). Sunscreens suppress cutaneous vitamin D synthesis. *Journal of Clinical Endocrinology and Metabolism*, *64*(6), 1165-1168.
- McNally, J. D., Leis, K., Matheson, L. A., Karuananyake, C., Sankaran, K., & Rosenberg, A. M. (2009). Vitamin D deficiency in young children with severe acute lower respiratory infection. *Pediatric Pulmonology*, *44*(10), 981-988.
- Morales, E., Romieu, I., Guerra, S., Ballester, F., Rebagliato, M., Vioque, J., . . . Sunyer, J. (2012). Maternal vitamin D status in pregnancy and risk of lower respiratory tract infections, wheezing, and asthma in offspring. *Epidemiology*, *23*(1), 64-71.
- Muhe, L., & Lulseged, S. (1997). Case-control study of the role of nutritional rickets in the risk of developing pneumonia in Ethiopia. *Lancet*, *349*(9068), 1801-1804.

- Najada, A. S., Habashneh, M.S., & Khader, M. (2004). The frequency of nutritional rickets among hospitalized infants and its relation to respiratory diseases. *Journal of Tropical Pediatrics*, 50(6), 364-368.
- National Institutes of Health. (2011). Dietary supplement fact sheet: Vitamin D. Retrieved from <http://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/>
- Nguyen, M., Trubert, C. L., Rizk-Rabin, M., Rehan, V. K., Besançon, F., Cayre, Y. E., & Garabédian, M. (2004). 1,25-Dihydroxyvitamin D₃ and fetal lung maturation: Immunogold detection of VDR expression in pneumocytes type II cells and effect on fructose 1,6 bisphosphatase. *Journal of Steroid Biochemistry and Molecular Biology*, 89-90, 93-97.
- Nobel Foundation. (1903). Niels Ryberg Finsen—Biography. Retrieved from http://www.nobelprize.org/nobel_prizes/medicine/laureates/1903/finsen-bio.html
- Pelletier, A. J., Mansbach, J. M., & Camargo, C. A. (2006). Direct medical costs of bronchiolitis hospitalizations in the United States. *Pediatrics*, 118(6), 2418-2423.
- Rehan V. K., Torday J. S., Peleg S., Gennaro, L., Vouros, P., Padbury, J., ... Reddy, G. S. (2002) 1Alpha,25-dihydroxy-3-epi-vitamin D₃, a natural metabolite of 1alpha,25-dihydroxy vitamin D₃: Production and biological activity studies in pulmonary alveolar type II cells. *Molecular Genetics and Metabolism*, 76, 46-56.
- Roelandts, R. (2002). The history of phototherapy: Something new under the sun? *Journal of the American Academy of Dermatology*, 46(6), 926-930.
- Roth, D. E., Jones, A. B., Prosser, C., Robinson, J. L., & Vohra, S. (2009). Vitamin D status is not associated with the risk of hospitalization for acute bronchiolitis in early childhood. *European Journal of Clinical Nutrition*, 63(2), 297-299.

- Roth, D. E., Shah, R., Black, R. E., & Baqui, A. H. (2010). Vitamin D status and acute lower respiratory infection in early childhood in Sylhet, Bangladesh. *Acta Paediatrica*, 99(3), 389-393.
- Salimpour, R. (1975). Rickets in Tehran. *Archives of Disease in Childhood*, 50: 63-65.
- Wagner, C. L., & Greer, F. R. (2008). Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics*, 122(5), 1142-1152.
- Wayse, V., Yousafzai, A., Mogale, K., & Filteau, S. (2004). Association of subclinical vitamin D deficiency with severe acute lower respiratory infection in Indian children under 5 y. *European Journal of Clinical Nutrition*, 58(4), 563-567.
- Winterstein, A., Hampp, C., & Saidi, A. (2012). Effectiveness of palivizumab prophylaxis in infants and children in Florida. *Pharmacoepidemiology and Drug Safety*, 21(1), 53-60.