2014-10-18

Vitamin D Deficiency and Acute Lower Respiratory Infections in Children Younger Than 5 Years: Identification and Treatment

Allison Larkin

Jane H. Lassetter
Brigham Young University - Provo, jane_lassetter@byu.edu

Vitamin D Deficiency and Acute Lower Respiratory Infections in Children Younger Than 5 Years: Identification and Treatment CE

Allison Larkin, MS, NP-C, & Jane Lassetter, PhD, RN

ABSTRACT

Introduction: Acute lower respiratory infection (ALRI) is a leading cause of childhood mortality. Research suggests that vitamin D deficiency (VDD) puts children at risk for ALRI. The purpose of this review is to examine ALRI and VDD in children 5 years and younger. Common etiologies, diagnosis, prevention, treatment of ALRI, and recommendations for vitamin D supplementation are summarized.

Method: Databases were searched for studies investigating VDD and ALRI in children. Independent reviewers assessed the internal validity of the studies.

Results: Of 18 studies examined, VDD was found to be associated with increased risk or severity of ALRI in 13 studies; associations were not found in 4 studies. In one study it was found that high maternal vitamin D levels was associated with ALRI in infants.

Discussion: Vitamin D supplementation is a low-cost, low-risk intervention that providers should consider for children, especially those at high risk for ALRI. Practitioners should follow current recommendations when prescribing vitamin D supplementation for infants and children. J Pediatr Health Care. (2014) 28, 572-582.

Allison Larkin, Nurse Practitioner, Physical Medicine and Rehabilitation, The Children's Hospital of Philadelphia, Philadelphia, PA.

Jane Lassetter, Associate Professor, Brigham Young University, Provo, UT.

Conflicts of interest: None to report.

Correspondence: Allison Larkin, MS, NP-C, Physical Medicine and Rehabilitation, The Children's Hospital of Philadelphia, 3401 Civic Center Blvd, Philadelphia, PA 19104; e-mail: LarkinA@email.chop.edu.

KEY WORDS

Vitamin D, acute lower respiratory infection, pneumonia, bronchiolitis

OBJECTIVES

1. Explain the physiology of vitamin D synthesis.
2. Describe the etiology, diagnosis, prevention, and treatment of acute lower respiratory infections (ALRIs).
3. Discuss the possible associations between vitamin D deficiency and ALRI.
4. Describe the current recommendations for vitamin D intake during pregnancy, lactation, and childhood.
5. State the dosing recommendations for the supplementation of vitamin D in children.
6. Describe the adverse effects of vitamin D supplementation and toxicity.

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 an increasingly popular treatment for tuberculosis (Roelandts, 2002). It was thought that the efficacy of phototherapy might be due to sunlight increasing vitamin D levels. After the discovery of antibiotics, light intervention was abandoned. However, more than a century later, the possibilities of vitamin D for prevention and treatment of respiratory illnesses are now being researched again (Camargo et al., 2011; Manaseki-Holland et al., 2010).

A possible connection between vitamin D deficiency (VDD) and respiratory infections has been proposed. 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 that 43% also had pneumonia. Research also has associated VDD with acute lower respiratory tract infection (ALRI), which includes bronchiolitis and pneumonia (Karatekin, Kaya, Salihoğlu, Balci, & Nuhoğlu, 2009; Roth, Shah, Black, & Baqui, 2010).

The association between ALRI and VDD is important because ALRI is costly and a leading cause of global child mortality, annually accounting for approximately 1.4 million deaths of children younger than 5 years (Black et al., 2010). Globally in 2010, there were an estimated 15 million hospitalizations of children with severe or very severe ALRI (Nair et al., 2013). In the United States, hospitalization costs for respiratory syncytial virus (RSV) infections, a common cause of bronchiolitis, range from an average of $5069 for children without underlying comorbidity to an average of $12,103 for children with chronic lung disease (Hampp, Kauf, Saidi, & Winterstein, 2011). If vitamin D could prevent ALRI or decrease the duration and/or severity of ALRI in children, it could save lives and decrease health care costs. Therefore, the purposes of this review are threefold: to describe the etiology, diagnosis, prevention, and treatment of ALRI; to conduct a review of literature regarding the association between VDD and ALRI in children 5 years of age or younger; and to make recommendations for health care providers regarding vitamin D supplementation to prevent or lessen severity of ALRI in children 5 years of age or younger.

> If vitamin D could prevent ALRI or decrease the duration and/or severity of ALRI in children, it could save lives and decrease health care costs.

ETIOLOGY, DIAGNOSIS, PREVENTION, AND TREATMENT OF ALRI

The term ALRI encompasses both bronchiolitis and pneumonia. Although both are lower respiratory tract infections, they are separate diseases with etiological differences.

Etiology

Bronchiolitis occurs when viruses infect bronchiolar epithelial cells, causing damage and inflammation in the bronchioles. RSV is the most common cause of bronchiolitis, but other causes also exist, including parainfluenza virus, adenovirus, rhinovirus, human metapneumonovirus, coronavirus, and bocavirus (Pavia, 2011). Bronchiolitis is highly contagious and spreads through direct contact with nasal secretions, airborne droplets, and fomites, which are contaminated surfaces that aid the spread of viral infections. RSV bronchiolitis often leads to a secondary bacterial infection and pneumonia (Thorburn, Harigopal, Reddy, Taylor, & van Saene, 2006).

Pneumonia is an inflammation of the lung parenchyma, consolidation in the affected area, and filling of alveolar air spaces with exudate and inflammatory cells. It may be caused by viruses, bacteria, or a mixed bacterial and viral infection. The most common viral and bacterial causes of pneumonia are listed in Table 1 (Cevey-Macherel et al., 2009). *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are considered atypical pathogens.

Diagnosis

The diagnosis of bronchiolitis is primarily clinical. The American Association of Pediatrics (AAP, 2006) defines bronchiolitis as a set of clinical signs and symptoms, including initial viral upper respiratory manifestations followed by increased respiratory effort and wheezing in children younger than 2 years. Signs of increased respiratory effort include tachypnea, nasal flaring, and chest retractions. Current evidence does not support obtaining routine chest radiography for children with bronchiolitis (AAP, 2006).

Signs and symptoms of pneumonia are similar to those of bronchiolitis: fever, tachypnea, and respiratory distress. On examination, decreased lung sounds, crackles, tactile fremitus, and dullness to percussion are consistent with pneumonia-induced consolidation. The presence of an infiltrate on chest radiograph is used to confirm pneumonia (Barson, 2014).

Prevention and Treatment

Prevention of ALRI is limited primarily to hand washing and minimizing exposure to bacteria and viruses that cause respiratory infections. Palivizumab (Synagis) is a vaccine that has been shown to be effective in preventing RSV in infants at high risk for

TABLE 1. Common etiologies of acute lower respiratory infection

Disease	Pathogen
Bronchiolitis	RSV
	Parainfluenza
	Adenovirus
	Rhinovirus
	Human metapneumovirus
	Coronavirus
	Bocavirus
Viral pneumonia	Influenza
	Parainfluenza
	Adenovirus
	RSV
	Human metapneumovirus
Bacterial pneumonia	*Streptococcus pneumoniae*
	Group A beta-hemolytic streptococcus
	Mycoplasma pneumoniae[*]
	Chlamydia pneumoniae[*]

Note. *RSV = respiratory syncytial virus. Data from Cevey-Macherel, M., Galetto-Lacour, A., Gervaix, A., Siegrist, C., Bille, J., Bescher-Ninet, B. … Gehri, M. (2009). Etiology of community-acquired pneumonia in hospitalized children based on WHO clinical guidelines.* European Journal of Pediatrics, 168*(12), 1429–1436 and Pavia, A. T. (2011). Viral infections of the lower respiratory tract: Old viruses, new viruses and the role of diagnosis.* Clinical Infectious Diseases, 52*(Suppl 4), S284–S289.
[*]Atypical causes.

complications (Winterstein, Hampp, & Saidi, 2012). According to the most recent policy on palivizumab of the AAP Committee on Infectious Diseases (2009), high-risk infants should receive palivizumab once a month for a maximum of 5 months during RSV season until they reach 24 months of age, and other premature infants who qualify for prophylaxis should receive palivizumab monthly for a maximum of 3 months during the RSV season. Palivizumab dosage is 15 mg per kg (AAP Committee on Infectious Diseases, 2009) and costs on average $1074 per 50-mg vial (Mahadevia, Masaquel, Polak, & Weiner, 2012), making the treatment cost for a 3-kg infant approximately $966 for a single dose of palivizumab, or approximately $5000 for 5 months' administration early in life. As the child grows, so does the dose required. In the second year of life, the cost can be $3000 per month (for a child who weighs more than 10 kg) or up to $15,000 for 5 months of the RSV season (Hampp et al., 2011). In Florida's Medicaid population, Hampp and associates (2011) concluded that the cost of palivizumab prophylaxis to prevent RSV-related hospitalizations "far exceeded the savings associated with prevented hospitalizations" (p. 502). This cost-benefit analysis highlights the need to identify less costly ways to prevent and treat RSV-related ALRIs.

Current treatment of ALRI is mostly supportive. Nasopharyngeal suctioning, oxygen therapy, intravenous fluids, and antipyretic agents might be used. Antibiotics and antiviral drugs are sometimes administered whether the infection is thought to be bacterial or viral (Kabra, Lodha, & Pandey, 2010).

VITAMIN D AND VITAMIN D DEFICIENCY

Vitamin D, an essential steroid hormone, is primarily synthesized in the skin and liver from sun exposure, but it can also be obtained through dietary intake or supplements (Holick, 2007). Both lower and upper limits of healthy serum vitamin D levels are unclear. The Institute of Medicine (IOM, 2011) defines VDD as a serum level less than 20 ng/ml, but in research studies the threshold for VDD varies widely (Holick, 2007). Researchers have questioned whether current recommendations of vitamin D intake are sufficient for optimal health outcomes (Bischoff-Ferrari, Giocannucci, Willett, Dietrich, & Dawson-Hughes, 2006; Mansbach, Ginde, & Camargo, 2009).

Although vitamin D is fairly simple to obtain, an estimated 1 billion people worldwide have vitamin D insufficiency (21-29 ng/ml) or deficiency (Holick, 2007). Cultural and health practices can contribute to vitamin D insufficiency or VDD by preventing infants from acquiring vitamin D from sun exposure. First, in some cultures infants are swaddled when outdoors, minimizing their sun exposure (Najada, Habashneh, & Khader, 2004). Second, applying sunscreen to limit the sun's damage to skin is recommended, especially in children, because 25% of lifetime sun exposure is estimated to occur before 18 years of age, a time of high vulnerability to the potentially toxic effects of sun exposure (Balk & AAP, Council on Environmental Health and Section on Dermatology, 2011). However, sunscreen suppresses cutaneous synthesis of vitamin D3 by blocking the absorption of ultraviolet 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 (Lee et al., 2007). At its best, breast milk provides little vitamin D and even less if a mother is vitamin D deficient (Wagner & Greer, 2008).

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 (Shoben et al., 2011). Interestingly, researchers have found associations between VDD and seasonal respiratory illnesses, such as upper respiratory infections (Ginde, Mansbach, & Camargo, 2009). Grant (2008) hypothesized that sun exposure and its effect on vitamin D levels could help explain the seasonality of childhood respiratory infections, such as bronchiolitis or pneumonia, which peak in the winter when sunlight is scarce and dissipate in the summer.

METHODS

Identification of Studies

An electronic search was conducted to identify studies from 2004-2014 in the following databases: Medline, CINAHL, and the Cochrane Library. 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. We included one classical study published prior to 2004 (Muhe & Lulseged, 1997). 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 older than 5 years of age or focused on asthma. 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 controlled trials.

Conversion of Measurement and VDD Definitions

The thresholds for determining VDD vary widely, from 9 to 20 ng/ml. This variation makes it difficult to compare findings of the studies. Further adding to comparison challenges, two different units of measurement were used in the reviewed studies to assess vitamin D levels: nanomole per liter and nanogram per milliliter. We converted all values to nanograms per milliliter 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 nanomoles per liter were multiplied by 0.4 to convert to nanograms per milliliter.

Assessment of Internal Validity

The two authors independently assessed the studies' internal validity using the United States Preventive Services Task Force (USPSTF) criteria (Harris et al., 2001). Each study is given a rating of good, fair, or poor based on the criteria for the specific type of study (Table 2). A good study meets all criteria listed, a fair study fails to meet all criteria but does not have a fatal flaw, and a poor study contains a fatal flaw.

Review of Literature

Internal validity of the studies was assessed. Major topics of the reviewed studies included rickets and ALRI, the correlation between VDD and ALRI, the severity of ALRI, and the effect of vitamin D on the immune system.

Internal Validity of Studies

Using the USPSTF criteria, the authors rated the internal validity of each of studies included in the literature review 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.

RESULTS

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 radiograph. First, in a matched case-control study in the Ethio-Swedish Children's Hospital in Ethiopia, rickets was significantly more prevalent among the 500 children younger than 5 years of age admitted with pneumonia than it was among the 500 control subjects with no evidence of pneumonia (210 vs. 20, matched odds ratio 22.11, $p < .0001$; Muhe & Lulseged, 1997). However, these researchers did not find an increase in mortality of children with pneumonia and rickets compared with children who only had pneumonia (relative risk [RR] 1.16, $p = .20$). Second and similarly, Najada and colleagues (2004) conducted a study involving 443 infants aged 0 to 24 months in Amman, Jordan, and found that significantly more rachitic infants were admitted with lower respiratory tract diseases than were nonrachitic control subjects (85% vs. 30%, $p < .01$). The length of hospital stay was significantly longer for rachitic infants than for nonrachitic infants (9.5 days vs. 7.4, $p = .002$).

In the study by Muhe and Lulseged (1997), 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 control subjects (13.37, $p < .001$). The rachitic and nonrachitic children in the study by Najada and colleagues (2004) also differed significantly in the birth order of the child, family size, mode of feeding, outdoor dressing of mothers (covering the body with thick, dark clothing), and the presence of anemia; however, Najada and colleagues 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 the correlation between infant vitamin D levels and ALRI. In two studies it was found that 25(OH)D levels were significantly lower in infants with ALRI than in control subjects (Karatekin et al., 2009; Roth et al., 2010). Karatekin and colleagues (2009) studied 25 newborns with ALRI and 15 healthy newborn control subjects in Istanbul, Turkey, and found that newborns (within the first 28 days of life) with ALRI had significantly lower serum

TABLE 2. 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/control subjects with exclusion criteria applied equally to both
	Response rate
	Diagnostic testing procedures applied equally to each group
	Appropriate attention to potential confounding variables
RCTs 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

Note. *RCT = randomized controlled trial. From 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. Reprinted with permission.*

25(OH)D concentrations than did control newborns (9.12 ± 8.88 ng/ml vs. 16.33 ± 13.42 ng/ml, p = .011). Roth and colleagues (2010) had similar results when comparing 25 case-control pairs in Sylhet, Bangladesh. The cases, children 1 to 18 months of age who were hospitalized with ALRI, were matched to control subjects based on age, sex, and village. In their study, the mean serum 25(OH)D of the cases was significantly lower than that of the control subjects (11.6 vs. 15.6 ng/ml, p = .015).

In three studies an association also was found between infant ALRI and cord blood or maternal vitamin D levels. In a prospective birth cohort study of 156 infants in the Netherlands, Belderbos and colleagues (2011) found that low levels of vitamin D in the cord blood increased the risk of RSV within the first year of life. Infants with a 25(OH)D cord blood level < 20 ng/ml had an adjusted relative risk of 6.2 compared with infants who had a 25(OH)D cord blood level ≥ 30 ng/ml (95% confidence interval [CI], 1.6-24.9; p = .01). Camargo and colleagues (2011) conducted a similar study in New Zealand and found that in newborns with 25(OH)D cord blood levels < 10 ng/ml, respiratory infections were twice as likely to develop by 3 months of age compared with 3-month-old infants who had 25(OH)D cord blood levels ≥ 30 ng/ml

(adjusted odds ratio [OR], 2.04) as newborns. Likewise, Morales and colleagues (2012) studied 1693 children younger than 5 years of age in Spain and found that 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: OR, 0.67; 95% CI, 0.50-0.90; p = .016).

Not all researchers found a decrease in ALRI with increased vitamin D levels. Roth, Jones, Prosser, Robinson, and Vohra (2009) conducted a study in Alberta, Canada, and did not find a significant difference in VDD between 64 cases of ALRI and 65 control subjects without a history of hospitalization for ALRI, using either the 25(OH)D threshold of < 16 ng/ml (4.7 vs. 1.5%, p = .365) or < 32 ng/ml (51.6 vs. 56.9%, p = .598). McNally and colleagues (2009) similarly found no difference in mean vitamin D levels between 105 children with ALRI and 92 control children in Saskatchewan, Canada (32.4 ± 15.6 vs. 33.2 ± 12.0 ng/ml, p = .71). However, the difference in prevalence of 25(OH)D levels < 20 ng/mL between the pneumonia subgroup and control subjects was approaching significance (30% vs. 16%, p = .07). In a secondary analysis of the same data, Leis and colleagues (2012) found that children with a vitamin D intake of less than 80 IU/kg/day were more than four times more likely to have

ALRI compared with children who had a vitamin D intake exceeding 80 IU/kg/day (OR, 4.9; CI, 1.5-16.4). Also while studying dietary intake of vitamin D, Camargo and colleagues (2007) conducted research on 1194 mother-child pairs in Massachusetts and did not find an association between mothers' intake of vitamin D and their infants' risk of respiratory infection (p = .09). The children were enrolled in the study at birth, and respiratory infection status was evaluated at 6 months, 12 months, and 24 months.

Severity of ALRI

Some researchers investigated the role of vitamin D in the severity of ALRI in children. In a case-control study in India, Wayse, Yousafzai, Mogale, and Filteau (2004) found that serum 25(OH)D levels > 9 ng/ml was associated with a significantly lower risk of severe ALRI (OR, 0.09; 95% CI, 0.03-0.24; p < .001). In a study of 152 children younger 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 (p = .021; Banajeh, 2009). Rachitic children were four times more likely than non-rachitic children to fail to respond to treatment 30 days after enrollment in the study (20.6 vs. 6%; 95% CI, 1.2-14.4; p = .029). Treatment failure was defined as modification of treatment because of worsening clinical condition, development of a comorbid condition, such as bacterial meningitis, or death. Likewise, Inamo and colleagues (2011) studied 28 infants in Tokyo, Japan, and found that, compared with infants who had 25(OH)D levels of 6 ng/ml or more, infants with 25(OH)D levels of < 4 ng/ml were significantly more likely to need supplementary oxygen and ventilator management (p < .01). Similarly, McNally and colleagues (2009), previously discussed, found that children with ALRI in a Canadian pediatric intensive care unit had significantly lower vitamin D levels than did control subjects, who were children hospitalized for something other than ALRI (19.6 ± 9.6 vs. 33.2 ± 12.0 ng/ml, p = .001). These studies suggest that VDD might increase the severity of a respiratory infection and that 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. In a double-blind randomized controlled trial in inner-city Kabul, Afghanistan, baseline vitamin D levels were not measured, but researchers compared oral vitamin D supplementation with placebo in 224 children with pneumonia. They found 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 = .17; Manaseki-Holland et al., 2010). Additionally, Carroll and colleagues (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 and colleagues did not find a significant association between the maternal 25(OH)D level and the infants' bronchiolitis score (adjusted OR, 0.76; 95% CI, 0.52-1.11). Infant vitamin D levels were not measured in the study.

In contrast, Gale and colleagues (2008) found an association between high prenatal 25(OH)D levels and subsequent increased incidence of ALRI in the mothers' infants. In their study, conducted in Southampton, United Kingdom, they compared mothers in late pregnancy who were in the lowest quarter of 25(OH)D levels with counterparts in the highest quarter of 25(OH)D levels and found that mothers in the highest quarter were significantly more likely to report a diagnosis of pneumonia or bronchiolitis in their infants (OR, 4.80; 95% CI, 1.01-22.73). Infants' 25(OH)D levels were not evaluated. The study by Gale and colleagues (2008) was the only study located that found an association between high prenatal vitamin D level and an increased risk of ALRI in infants.

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 that VDD significantly decreased the percentage of circulating polymorph nuclear neutrophils (37% vs. 47%; adjusted OR, 0.71; 95% CI, 0.53-0.95; p = .02), which are important innate immune cells that migrate into the lung tissues and kill bacteria and viruses through phagocytosis. In a randomized controlled trial conducted in Afghanistan by Manaseki-Holland and colleagues (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 and associates (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 with children who received a placebo (92 vs. 122; RR, 0.78; 95% CI, 0.64-.94; p=.01). These results suggest vitamin D supplementation might strengthen the immune system. Because Manaseki-Holland and colleagues (2010) did not assess vitamin D levels, it is not known whether the children had VDD.

In the double-blind randomized controlled trial by Manaseki-Holland and associates (2012) in Afghanistan, 3046 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. These investigators did not find a significant difference in incidence of pneumonia between

the placebo group (0.137 per child per year; 95% CI, 0.121-0.155) and the vitamin D group (0.145 per child per year; 95% CI, 0.129-0.164).

During three previously discussed studies (Manaseki-Holland et al., 2010; Manaseki-Holland et al., 2012; and Najada et al., 2004), 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 adverse effects from vitamin D supplements administered to their children.

DISCUSSION
Limitations of Studies
All studies have limitations, and the studies reviewed were no exception. The limitations included lack of a consistent unit of measurement and thresholds, weaknesses in research methods, inconsistencies in control groups, not reporting the season of the study, and viral versus bacterial cause.

Lack of consistent unit of measurement and thresholds
Comparing results from the studies was difficult because they varied in unit of measurement and definition of VDD. Some studies did not define VDD. When VDD was defined, either nanogram per milliliter or nanomole per liter was the unit of measurement. As needed, we converted vitamin D values to nanogram

per milliliter to facilitate comparison between studies. In addition, researchers used thresholds ranging from 9 to 20 ng/ml to determine VDD (see Table 3). This range could explain why some studies found that VDD was significantly associated with ALRI in children, but 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 control subjects.

Weaknesses in Research methods
Different results might also be explained by lack of rigor in assessment tools. Gale and colleagues (2008) and Camargo and associates (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 and colleagues (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 reporting illnesses would reflect poorly on their abilities as mothers and be less socially acceptable (Lau, Hurst, Smith, & Schanler, 2007).

Bronchiolitis scores were used exclusively to assess illness severity in the study by Carroll and colleagues (2011), and individual scores were based on respiratory symptoms at one point in time. Trends in bronchiolitis scores are helpful in determining illness trajectory and

TABLE 3. Definitions of vitamin D sufficiency, insufficiency, and deficiency 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 et al. (2009)		< 16	< 10
Wayse et al. (2004)			< 9

Note. VDD = vitamin D deficiency; VDI = vitamin D insufficiency; VDS = vitamin D sufficiency. 25-hydroxyvitamin D (25[OH]D) is a biomarker of vitamin D status in circulation (Roth et al., 2010, p. 289).

effectiveness of respiratory treatments. However, the researchers used a single bronchiolitis score for each child, which does not accurately reflect the extent or severity of illness over time. Additionally, Carroll and colleagues did not specify when the bronchiolitis score was determined, and scores can vary widely, depending on the timing of assessment (e.g., on admission versus prior to discharge) and when the infant had last undergone suctioning or received a respiratory treatment. These data collection methods have weaknesses that could affect the study's results.

Another weakness is the lack of data on serum vitamin D levels. Neither randomized controlled trial (Manaseki-Holland et al., 2010; Manaseki-Holland et al., 2012) measured serum vitamin D levels either prior to administering vitamin D supplementation or after administration. Without these data, the participants' initial vitamin D status and the impact of supplementation are unknown.

Control group

Researchers of the case-control studies differed on the criteria used for control participants. Some researchers recruited control subjects 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 and colleagues (2010) used population-based sampling to find control subjects with no history of ALRI from the same villages as the cases in their study. In contrast, other researchers used control subjects who were children admitted to the hospital for illnesses other than ALRI (McNally et al., 2009; Muhe & Lulseged, 1997). Because of the effect that 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 the results.

Season of study

The season during data collection might also limit generalizability of the studies. Belderbos and colleagues (2011) found that 25(OH)D concentrations had a seasonal distribution, with the maximum point in July and the 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 situation could be a confounding factor that did not seem to be considered in some studies.

Bacterial versus viral cause

Another factor potentially affecting the results of the studies is whether the ALRI was caused by a bacteria or virus. Roth and colleagues (2009) found no difference between cases and control subjects in prevalence of vitamin D insufficiency in Canada. In contrast, Wayse and colleagues (2004) found adequate serum vitamin D to be associated with a lower risk of ALRI in India. Roth and colleagues (2009) suggested that the causative agent might explain the difference in findings between their study and the study by Wayse and associates (2004), noting that bacterial pneumonia is common in developing countries like India, but the study by Roth and associates (2009) in Canada included mostly patients with viral ALRI. Vitamin D might have a different effect on bacterial versus viral ALRI.

Treatment of Vitamin D Deficiency

Maternal and Child vitamin D

Because research indicates a possible association between low vitamin D and ALRI in children younger than 5 years old, maintaining both maternal vitamin D levels during pregnancy and the infants' own vitamin D levels might be protective against ALRI. The IOM and AAP have made recommendations regarding vitamin D intake. For pregnant and lactating women, a daily intake of 600 IU vitamin D per day is recommended (IOM, 2011). Most prenatal vitamins contain 400 IU vitamin D. For all breastfed infants, the AAP recommends a 400 IU vitamin D supplement daily beginning soon after birth for all breastfed infants, as well as children who consume less than 1 L of vitamin D–fortified formula or milk per day and adolescents who obtain less than 400 IU vitamin D per day through vitamin D–fortified milk or foods (Wagner & Greer, 2008). Vitamin D supplementation forms for infants and children are listed in Table 4 (Casey et al., 2010). Of note, there is a discrepancy between the multivitamin dose manufacturers recommend for 2- and 3-year-old children (1/2 tablet, 200 IU) and the amount of vitamin D the AAP recommends for vitamin D supplementation (400 IU).

Although further research is needed, health care providers should discuss vitamin D intake during well-child visits and encourage supplementation, especially for pregnant women and children, and in accordance

> …health care providers should discuss vitamin D intake during well-child visits and encourage supplementation, especially for pregnant women and children, and in accordance with current guidelines.

TABLE 4. Vitamin D supplementation forms for infants and children

Population	Brand	Recommended daily dose and vitamin D concentration
Breastfed infants and children younger than 2 years	Enfamil Poly-Vi-Sol	1 ml contains 400 IU
	Carlson Baby D	1 drop contains 400 IU
	Just D	1 ml contains 400 IU
	Twinlab Infant Care Multivitamin Drop	1 ml contains 400 IU
Children who consume less than 1 L vitamin D–fortified milk per day and adolescents who do not obtain 400 IU vitamin D per day through vitamin D-fortified milk and foods	Centrum Kids Complete Multivitamin, chewable	One tablet for children 4 years and older, contains 400 IU; ½ tablet for children 2 and 3 years of age
	Flintstone Children's Complete Multivitamin, chewable	One tablet for children 4 years and older, contains 400 IU; ½ tablet for children 2 and 3 years of age
	Flintstone Gummies with Calcium and Vitamin D, multivitamin	Two gummies for children 4 years and older, each gummy contains 200 IU; one gummy for children 2 and 3 years of age
	Disney Gummies Children's Multivitamin	Two gummies for children 2 years and older; each gummy contains 200 IU

Data used with permission from Casey, C. F., Slawson, D. C., & Neal, L. R. (2010). Vitamin D supplementation in infants, children, and adolescents. American Family Physician, 81*(6), 745–748.*

with current guidelines. Most infants are not consuming adequate vitamin D according to the 2008 AAP guidelines. A study in 2010 found that only 5% to 13% of breastfed infants are receiving the recommended oral vitamin D supplements (Perrine, Sharma, Jefferds, Serdula, & Scanlon, 2010). Health care providers should also consider assessing vitamin D levels for children who have a risk factor for vitamin D deficiency, such as poor dietary vitamin D intake and/or limited sunlight exposure (Mithal et al., 2009), or for women who are pregnant or lactating (Holick, et al., 2011).

Cost

Health care providers should consider the cost of vitamin D supplementation. It is a relatively inexpensive and 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.

Adverse effects

Health care providers should also be aware of adverse 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 hypercalcemia

can be avoided if 25(OH)D levels are monitored and vitamin D dosage is adjusted accordingly. Health care providers should aware of these potential toxicity symptoms and watch for them in their patients.

Adequacy of current supplements

For pregnant or lactating women, the IOM (2011) established 600 IU of vitamin D per day as adequate. Currently, most prenatal vitamins only contain 400 IU of vitamin D, so this might not be enough vitamin D in prenatal vitamins. 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, approximately 6.5 times the IOM's recommendation. These findings suggest an implication for policy, which would be to increase the recommended amount of vitamin D in prenatal vitamins.

Vitamin D Fortification

Another implication of these findings is the need for vitamin D–fortified food 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, fortifying foods commonly eaten by infants could prevent both rickets and ALRI.

IMPLICATIONS FOR RESEARCH

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

CONCLUSION

VDD was prevalent among both mothers and infants in multiple studies. In several of the studies it was found that VDD was associated with increased risk for ALRI (Banajeh, 2009; Belderbos et al., 2011; Camargo et al., 2011; Inamo et al., 2011; Karatekin et al., 2009; Manaseki-Holland et al., 2010; McNally et al., 2009; Morales et al., 2012; Muhe and Lulseged, 1997; Najada et al., 2004; Roth et al., 2010; Wayse et al. 2004); however, a few did not find an association between VDD and ALRI (Camargo et al., 2007; Carroll et al., 2011; Gale et al., 2008; Manaseki-Holland et al., 2012; Roth et al., 2009). More research is needed to determine the role that vitamin D plays in the prevention and treatment of ALRI and the impact supplementation can have. However, vitamin D supplementation is a low-cost, low-risk intervention that providers should consider for children, especially those at high risk for ALRI.

REFERENCES

American Academy of Pediatrics Committee on Infectious Diseases. (2009). Policy statement— Modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics, 124*(6), 1694-1701.

American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. (2006). Diagnosis and management of bronchiolitis. *Pediatrics, 118*(4), 1774-1793.

Balk, S. J., & American Academy of Pediatrics, Council on Environmental Health and Section on Dermatology. (2011). Ultraviolet radiation: A hazard to children and adolescents. *Pediatrics, 127*(3), 588-597.

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.

Barson, W. J. (2014). Community-acquired pneumonia in children: Clinical features and diagnosis. Retrieved from http://www.uptodate.com/contents/community-acquired-pneumonia-in-children-clinical-features-and-diagnosis

Belderbos, M. E., Houben, M. L., Wilbrink, B., Lentjes, E., Bloemen, E. M., Kimpen, J. 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.

Black, R. E., Cousens, S., Johnson, H. L., Lawn, J. E., Rudan, I., Bassani, D. G., … Mathers, C. (2010). Global, regional, and national causes of child mortality in 2008: A systematic analysis. *The Lancet, 375*(9730), 1969-1987.

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.

Casey, C. F., Slawson, D. C., & Neal, L. R. (2010). Vitamin D supplementation in infants, children, and adolescents. *American Family Physician, 81*(6), 745-748.

Cevey-Macherel, M., Galetto-Lacour, A., Gervaix, A., Siegrist, C., Bille, J., Bescher-Ninet, B., … Gehri, M. (2009). Etiology of community-acquired pneumonia in hospitalized children based on WHO clinical guidelines. *European Journal of Pediatrics, 168*(12), 1429-1436.

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.

Hampp, C., Kauf, T. L., Saidi, A. S., & Winterstein, A. G. (2011). Cost-effectiveness of respiratory syncytial virus prophylaxis in various indications. *Archives of Pediatric and Adolescent Medicine, 165*(6), 498-505.

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.

Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., … Weaver, C. M. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology and Metabolism, 96*(7), 1911-1930.

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-1758S.

Inamo, Y., Hasegawa, M., Saito, K., Hayashi, R., Ishikawa, T., Yoshino, Y., … Fuchigami, T. (2011). Serum vitamin D concentrations and associated severity of acute lower respiratory tract infections in Japanese hospitalized children. *Pediatrics International, 2011*(53), 199-201.

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 of Systematic Reviews, 3*, 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.

Lau, C., Hurst, N. M., Smith, E. O., & Schanler, R. J. (2007). Ethnic/racial diversity, maternal stress, lactation and very low birth-weight infants. *Journal of Perinatology, 2007*(27), 399-408.

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). Overview of disorders of calcium concentration. *Merck Manual Online*. Retrieved from http://www.merck manuals.com/professional/endocrine_and_metabolic_disorders/electrolyte_disorders/disorders_of_calcium_concentration.html#v1150427

Mahadevia, P. J., Masaquel, A. S., Polak, M. J., & Weiner, L. B. (2012). Cost utility of palivizumab prophylaxis among pre-term infants in the United States: A national policy perspective. *Journal of Medical Economics, 15*(5), 987-996.

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), 1419-1427.

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.

Mithal, A., Wahl, D. A., Bonjour, J. P., Burckhardt, P., Dawson-Hughes, B., Eisman, J. A., … Morales-Torres, J. (2009). Global vitamin D status and determinants of hypovitaminosis D. *Osteoporosis International, 20*(11), 1807-1820.

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.

Nair, H., Simões, A. F., Rudan, E., Gessner, B. D., Azziz-Baumgartner, E., Zhang, J. S. F., … Campbell, H. for the Severe Acute Respiratory Working Group. (2013). Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: A systematic analysis. *The Lancet, 381*, 1380-1390.

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/

Nobel Foundation. (1903). Niels Ryberg Finsen—Biography. Retrieved from http://www.nobelprize.org/nobel_prizes/medicine/laureates/1903/finsen-bio.html

Pavia, A. T. (2011). Viral infections of the lower respiratory tract: Old viruses, new viruses and the role of diagnosis. *Clinical Infectious Diseases, 52*(Suppl 4), S284-S289.

Perrine, C. G., Sharma, A. J., Jefferds, M. E., Serdula, M. K., & Scanlon, K. S. (2010). Adherence to vitamin D recommendations among US infants. *Pediatrics, 125*(4), 627-632.

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.

Shoben, A. B., Kestenbaum, B., Levin, G., Hoofnagle, A. N., Psaty, B. M., Siscovick, D. S., & Boer, I. H. (2011). Seasonal variation in 25-hydryxyvitamin D concentrations in the Cardiovascular Health Study. *American Journal of Epidemiology, 174*(12), 1363-1372.

Thorburn, K., Harigopal, S., Reddy, V., Taylor, N., & van Saene, H. K. (2006). High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. *Thorax, 61*(7), 611-615.

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.