ORIGINAL PAPER

JMS Journal of Medical Science

Vitamin D3 in acute respiratory infections in patients under age five in a health institution in Colombia

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Keywords: vitamin D3, acute respiratory infection, insufficiency, deficiency

Published: 2022-08-01

How to Cite: Fontalvo-Rivera D, Mazenett E, Àlvarez-Zambrano C, Gómez-Camargo D. Vitamin D3 in acute respiratory infections in patients under age five in a health institution in Colombia. Journal of Medical Science. 2022;91(3);e679. doi:10.20883/medical.e679

DOI: https://doi.org/10.20883/medical.e679

ABSTRACT

Aim. describe the clinical behavior in acute respiratory infections in patients under age five in a Colombian health institution after VD3 administration. Clinical trials are required to determine this potential benefit.
Material and Methods. A performed series of 38 patients of both genders, aged 0-60 months to whom 50,000 units of VD3 were orrally administered per month for three months is described. The number of episodes, visits to the emergency room, and hospitalizations due to acute respiratory infections (ARI) before and after VD3 administration were described.
Results. The average age of the participants was 25.81 ± 17.50 months. The average number of ARI clinical events per month was 4.02 (95% CI 3.64-4.40) prior to VD3 administration. The number of episodes reduced at the end of the three cycles was 2.23/month (95% CI 1.81-2.65; p = 0.0230). The average number of emergency room visits during three months prior to the VD3 administration was 2.15 (95% CI 1.77-2.53). After three months of treatment, the average number of emergency room visits decreased to 0.52 (95% CI 0.32-0.72; p = 0.0180). Prior to VD3 administration, 31.58% required hospitalization. After the administration of three VD3 doses, only one patient required hospitalization (2.63%; $\overline{X}$:0.026 (95% CI 0.02-0.03; p = 0.0368).
Conclusions. Vitamin D3 administration could have a benefit in reducing the number of ARI episodes, emergency room visits, and hospitalalizations in children under age five.

Introduction

Acute respiratory infection (ARI) is among the most important causes of morbidity and mortality in children under age 5, ranking among the three leading causes of death worldwide in this age group [1, 2]. It represents one of the main causes of medical appointments and hospitalization in

this population group, originating between 40% and 60% of pediatric appointments in low income countries, and 20% to 40% of pediatric hospitalizations in most countries [3, 4].

The incidence and mortality due to acute respiratory infection is higher in low-income countries. There are several circumstances by which this predisposition can be increased in this group of countries where children under age 5 are the most affected [5, 6]. Among this circumstances, exists the difficulty in diagnosing lower ARI in young infants and the lack of education in caregivers to recognize the signs and symptoms of major disease [3, 7, 8]. Immunological immaturity of children under 5 makes them susceptible to an increase in morbidity and mortality from this group of diseases [3, 9, 10]. Given this, it is necessary to improve sociodemographic and nutritional conditions, as well as improving the response of the immune system to these diseases [10, 12]. The impact of micronutrient levels on respiratory infections has been described [13–15], among which is the closest association of vitamin D3 deficiency (VD3) with ARI risk [16–22]. Besides enhancing chemotaxis and phagocytic capabilities of innate immune cells, VD3 activates the transcription of antimicrobial peptides such as defensin β2 (DEFB) and cathelicidin antimicrobial peptide [23–28].

There is no consensus on the levels to conceptualize VD3 insufficiency or deficiency, although levels of at least 10 ng/ml are estimated to promote calcium mineralization and homeostasis, and a concentration between 20 to 50 ng/ml, for the immunomodulator effect [29, 30].

Aim

The objective of this work is to describe the clinical behavior in respiratory infections in a series of patients under age 5 in a Colombian health institution after VD3 administration

Material and Methods

A descriptive study was carried out in 38 patients of both genders, aged less than or equal to 5 years, who attended the pediatric outpatient clinic of the Policia Departmental of Bolívar for ARI attributed reasons, from February 1st to May 1st, 2018. The study was carried out in Cartagena de Indias, a warm-tropical climate city (ambient temperature 24° and 34°C) located in the Caribbean region of Colombia.

Exclusion Criteria

Patients who did not have informed consent from their parents, or guardians, and those with a history of hypersensitivity to VD3, or with pathologies in which VD3 administration is contraindicated were excluded from the study.

Definition of Terms and Classification Criteria

› The determination as an ARI case was made according to the definition proposed by the Atención Integrada a las Enfermedades Prevalentes en la Infancia (AIEPI) strategy (for its acronym Integrated Management of Childhood Illnesses-IMCI) of the World Health Organization (WHO) (**Table 1**). Classification according

Table 1. Definition and Classification According to Symptoms of Cough and/or Respiratory Difficulty of ARI

	BF (breaths/minute)	Age in months
No pneumonia	< 50	(2–11)
	< 40	(12–59)
	Without CR	
Nonsevere pneumonia	>50	(2–11)
	>40	(12–59)
	Without CR	
Severe pneumonia	With CR with or without tachypnea	
Very serious disease	Difficulty drinking, seizures, drowsiness, stridor, cyanosis	

Abbreviations: ARI, acute respiratory infection, an infectious process that can affect the nose, ears, pharynx, epiglottis, larynx, trachea, bronchioles or lungs, in which symptoms can be found that include cough, fever, odynophagia, earache, rhinorrhea, respiratory distress of an average duration of 7 to 14 days (34); BF, breathing frequency; CR, chest retractions; WHO: World Health Organization.

to the clinical status by symptoms of cough and respiratory distress was taken conforming to the WHO proposal [31, 32] (**Table 1**).

- To categorize patient as a type of upper or lower ARI tract, the classifications of the AIEPI strategy and the Colombian Ministry of Health were used [1] (**Table 2**).
- Classification of the socioeconomic stratum (SE) was carried out according to the criteria established by the Departamento Administrativo Nacional de Estadísticas de Colombia (DANE). Classification categories were defined as SE 1 which is referred to: SE as low – low, SE 2 as low, SE 3 as medium – low, SE 4 as medium, SE 5 as medium – high, and SE 6 as high [33].
- The states criterion of VD3 serum levels were determined according to the Practice Guide of the Society of Endocrinology [34] considering deficiency when the levels were less than 20 ng/ml, insufficiency between 21–29 ng/ml, sufficiency greater than 30 ng/ml, and intoxication greater than 150 ng/ml.
- Exposure to environmental pollution, humidity and house dust was realized by the location and housing conditions, and the type of food of the participants.
- Nutritional classification was made according to parameters established by resolution 2465 of 2016, using the Anthro program version 3.22.

Vitamin D Levels

Determination of serum vitamin D was performed using the LIAISON XL kit, immunochemiluminiscence analyzer, and the *LIAISON-25 OH Vitamin D TOTAL* Kit. This kit evaluates the serum levels of 25-hydroxyvitamin D Total, which corresponds to the sum of the fractions 25-OH-D2 and 25-OH-D3.

Supply of VD3

Patients were provided orally once a month for 3 months with two VD3 vials of 25,000 units (50,000 units) under the trade name of Histotal®, in the presence of the legal guardian and the investigator who had knowledge of the provided supplements. The vials were provided to participants in their original form.

Statistical Analysis

Data were entered into a database in the Microsoft Excel 2010 program. For univariate statistical analysis, Epi Info version 7.2.2.6 statistical software (*Centers for Disease Control and Prevention, Atlanta, Georgia, USA*) was used. Bivariate analysis was performed using Stata program software version 12.0 (*StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX*). Nominal type variables were presented using a frequency distribution. Confidence intervals were calculated for the estimates. Comparison of proportion differences in nominal qualitative variables were made using Fischer's exact test. Statistical significance was given for $p < 0.05$.

Ethical considerations

Study was submitted for evaluation by the audit committee of the Cartagena de Indias Medical Unit and the scientific subdirectorate of the National Police under the standards set forth in chapter I and II of Resolution 8430 of 1993 and the commitment to Good Practices. Clinic, consigned in resolution 2378 of 2008 (Colombia).

Table 2. Main Clinical Manifestations of ARI

ARI Type	Clinical Manifestations
ARI of upper respiratory tract	
Acute rhinopharyngitis	Fever, cough, rhinorrhea without respiratory difficulty for less than 14 days
Acute sinusitis	Fever, purulent rhinorrhea, halitosis, hyposmia for less than 2 weeks
Acute otitis media	Fever, otalgia for less than 2 weeks. Erythematous tympanic membrane, opaque, prominent or retracted with decreased mobility
Acute pharyngotonsillitis	Fever, odynophagia, erythema and pharyngo-tonsillar exudate, hypertrophy of tonsils, painful cervical lymphadenopathy (bacterial etiology)
ARI of lower respiratory tract	
Acute bronchiolitis	Initial catarrhal phase: fever, rhinorrhea, cough. Additional manifestations can include tachypnea, cough with cyanosis, refusal to feed, respiratory dyspnea, wheezing and/or crackles
Pneumonia acquired in the community (NAC)	Fever, cough, rhinorrhea, tachypnea for less than 15 days. Additional findings can include crackles and hypoventilation on pulmonary auscultation

Results

Of 93 eligible patients, 55 consented to participate. Seventeen patients were lost to follow-up, and 38 patients had definitive participation, with a distribution of 50% for both genders. The ages of the participants ranged from 4 to 60 months, with an average age of 25.81 ± 17.50 months (95% CI 19.23–30.81 months). Most of the participants belonged to a medium-low socioeconomic stratification (SE 3), with 25 patients (65.79%) (**Table 3**)

Clinical Features

Participants were exposed to house dust (16/38; 42.11%; 95% CI 26.31–59.18%), humid environments (18.42%; 95% CI 8.84–34.03%), smoking

Table 3. General Data on the Participants in the Study

		Basal status of VD3 serum levels	
	Total	Sufficiency	Insufficiency
Population, n (%)	38 (100)	31 (81.6)	7 (18.4)
Basal serum VD3 levels (ng/ml), average (SD)	38.7 (8.17)	41.5 (6.13)	26.4 (2.57)
Serum VD3 levels (ng/ml) after VD3 administration, average (SD)	49.0 (16.6)	51.8 (8.11)	36.3 (5.84)
Sex, n (%)			
Man	19 (50.0)	14 (45.2)	5 (71.4)
Woman	19 (50.0)	17 (54.8)	2 (28.6)
Age in months, average 95%CI	25.8 (19.2–30.8)	24.3 (18.0–30.6)	28.27 (9.0–47.6)
Socioeconomic stratification, n (%)			
2	6 (15.8)	5 (16.1)	1 (14.3)
3	25 (65.8)	21 (67.7)	4 (57.1)
4	7 (18.4)	5 (16.1)	2 (28.6)
Personal background, n (% / 95%CI)			
None	30 (79.0 / 62.7–90.5)	25 (80.7 / 62.5–92.6)	5 (71.4 / 29.0–96.3)
Malnutrition	2 (5.3 / 1.7–18.7)	1 (3.2 / 0.1–16.7)	1 (14.3 / 0.36–57.9)
Urinary infection	2 (5.3 / 1.7–18.7)	2 (6.5 / 0.8–21.4)	0 (0)
Otitis media	2 (5.3 / 1.7–18.7)	2 (6.5 / 0.8–21.4)	0 (0)
Idiopathic epilepsy	1 (2.6 / 1.1–14.5)	0/31 (0)	1 (14.29 / 0.36–57.9)
Adenoid hypertrophy	1 (2.6 / 1.1–14.5)	1 (3.2 / 0.1–16.7)	0 (0)
Respiratory background			
Environmental and nutritional exposure, n (%/95%CI)			
House dust	16 (42.1 / 26.3–59.2)	12 (38.7 / 21.8–57.8)	4/7 (57.14 / 18.4–90.1)
Humid climate	7 (18.4 / 8.8–34.0)	6 (19.4 / 7.5–37.5)	1 (14.3 / 0.4–58,0)
Intake chemical preservatives	5 (13.2 / 4.41–26.1)	5 (16.1 / 5.45–33.7)	0 (0)
Smoke	2 (5.3 / 2.6–17.8)	2 (6.5 / 0.8–21.4)	0 (0)
None	8 (21.0 / 9.6–37.3)	6 (19.4 / 7.5–37.5)	2 (28.6 / 3.7–71.0)
Respiratory disease background, n (% /95%CI)			
Allergic rhinitis	9 (23.7 / 11.4–40.2)	7 (22.58 / 9.6–41.1)	2 (28.6 / 0.36–57.9)
Asthma	7 (18.4 / 7.7–34.3)	7 (22.85 / 9.6–41.1)	0 (0)
None			
Hospitalization, n (%)	22 (57.9)	17 (54.8)	5 (71.2)
Acute bronchiolitis	14 (36.9)	12 (38.7)	2 (28.5)
Acquired pneumonia in the community	8 (21.1)	5 (16.1)	3 (42.9)
Number of times requiring hospitalization, n (%)			
Once	12 (31.6)		
Twice	2 (5.3)		
Anthropometric measures			
Men, average (95%CI)			
Weight in kg	13.6 (11.5–15.8)	14.3 (12.1–16.5)	8 (7.0–9.0)
IMC	16.2 (15.3–17.0)	16.1 (15.1–17.1)	16.75 (15.9–17.6)
Size in cm	91.2 (83.6–98.9)	93.8 (86.3–101.3)	69 (66.6–71.4)

Table 3 continued

	Basal status of VD3 serum levels		
	Total	Sufficiency	Insufficiency
Women, average (95%CI)			
Weight (Kg)	12.1 (10.1–14–2)	11.3 (9.0–13.7)	14.34 (9.6–19.1)
IMC	15.3 (14.7–16.1)	16.0 (14.9–16.3)	14.64 (12.8–16.5)
Size in cm	87.0 (79.2–94.7)	82.9 (74.2–91.7)	98.2 (83.3–113.2)
General z score, average (minimum SD -maximum SD)			
Weight/Age	0.45 (-1 to 3)	0.54 (-1 to 3)	0 (-1 to 2)
Weight/Size	0.11 (-2 to 2)	0.03 (-2 to 2)	-0.7 (-2 to 0)
IMC	0.03 (-2 to 3)	0.12 (-2 to 3)	-0.7 (-2 to 0)
Muscle-nutritional condition, n (% / 95%CI)			
Normal	30 (79.0 / 62.7–90.5)	25 (80.7 / 62.5–92.6)	5 (71.4 / 29.0–96.3)
Weight deficit	5 (13.2 / 4.4–28.1)	3 (9.7 / 2.0–25.8)	2 (28.6 / 3.67–71.0)
Overweight	3 (7.9 / 1.7–21.4)	3 (9.7 / 2.0–25.8)	0 (0)
Fitzpatrick skin phototype[a], n (%)			
Type IV Moderate Brown	19 (50.0)	16 (51.6)	3 (42.9)
Type III Light Brown	16 (42.1)	13 (41.9)	3 (42.9)
Type II White	2 (5.3)	1 (3.2)	1 (14.3)
Type V Dark Brown	1 (2.6)	1 (3.2)	0 (0)
Diagnostic impression, n (%)			
Acute rhinopharyngitis	20 (52.6)	16 (51.6)	4 (57.1)
Acute tonsillitis	4 (10.5)	3 (9.7)	1 (14.3)
Acute otitis media	4 (10.5)	3 (9.7)	1 (14.3)
Acute sinusitis	4 (10.5)	4 (12.9)	0 (0)
Acute bronchiolitis	3 (7.9)	3 (9.7)	0 (0)
Acquired pneumonia in the community	3 (7.9)	2 (6.5)	1 (14.3)
Serum calcium (mg/dl), average (95%CI)	10.1 (10.0–10.2)	10.1 (10.0–10.2)	10.0 (9.0–10.2)
Secondary effects of VD3 administration, n (%)			
Nausea	3 (7.9)	3 (9.7)	0 (0)
None	35 (92.1)	28 (90.3)	7 (100)

[a]Fitzpatrick Phototype Classification: I, pink and/or very pale skin, red or blonde hair, light eyes; II, light skin, blonde, red or light brown hair, light or brown eyes; III, intermediate light skin, hair and eyes of any color; IV, light brown skin, brown hair, brown eyes; V: dark brown skin, dark brown or black eyes and hair; VI: dark skin, dark brown or black eyes and hair (Marín D, Del Pozo A. Farmacia práctica. 2005;24(5):136-7)

(5.26%; 95% CI 2.64–17.75%), and intake of chemical preservatives (13.16%; 95% CI 4.41–26.09%) (**Table 3**).

As a history of respiratory pathologies, 9/38 patients suffered allergic rhinitis (23.68%; 95% CI 11.44–40.24%), and 7/38 suffered asthma (18.42%; 95% CI 7.74–34.33%). Fourteen (14/38) patients had a history of hospitalization for bronchiolitis (36.84%) and 8/38 for community-acquired pneumonia (CAP) (21.05%). Among other pathologies and previous conditions present in patients that could influence the development of ARI, are malnutrition (2/38; 5.56%; 95% CI 1.68–18.66%), acute otitis media (2/38; 5.56% 95% CI 1.68–18.66%), and hypertrophy adenoid (1/38; 2.63% 95% CI 1.07–14.53%) (**Table 3**), as well as family history such as asthma (7/38; 18.42% 95% CI 7.74–34.33%), and allergic rhinitis (9/38; 23.68% 95% CI 1.44–40.24%).

Nutritional status was normal in 30/38 patients (78.95%; 95% CI 62.68–90.45%), 5/38 had weight deficit (13.16%; 95% CI 4.41–28.09%), and 3/38 patients were overweight (7.89%; 95% CI 1.66–21.38%) (**Table 3**). In 10/38(26.32%) participants (95% CI 13.40–43.10%) breast milk was not given.

The influence that phototype could have on VD3 serum levels was determined by characterization according to the Fitzpatrick classification. The highest phototype found was type IV (moderate brown skin color) in 19/38 patients (50%; 95% CI 33.38–66.62%) (**Table 3**).

Respiratory examination findings varied according to ARI type. Hyaline rhinorrhea was

found more frequently (44.74%), followed by oropharyngeal erythema (13.16%) in those who had rhinopharyngitis and acute sinusitis. Tonsil hypertrophy with purulent exudate was found (10.53%) in patients with acute tonsilitis. Acute otitis media was more manifested with erythema and unilateral tympanic membrane bulging (10.53%). In cases with lower ARI respiratory tract, inspiratory wheezing was found (13.16%), and a patient presented use of accessory muscles (2.63%) requiring hospitalization under the diagnostic of pneumonia acquired in the community.

Imaging studies were not routinely requested. Chest X-ray was performed in four patients. Three presented a reticulonodular pattern (7.89%) and normality was reported in one of them (2.63%).

ARI Type

Of the 38 patients, 32 patients (84.21%; 95% CI 68.75–93.98%) had upper ARI respiratory tract symptoms discriminated in rhinopharyngitis in 20/38 patients (52.63%), acute tonsillitis in 4/38 patients (10.53%), acute otitis media in 4/38 (10.53%), and acute sinusitis in 4/38 patients (10.53%). Only 6/38 patients (15.79; 95% CI 6.02–31.25%) performed a lower presentation suggestive of ARI respiratory tract, including acute bronchiolitis in 3/38 patients (7.89%), and community-acquired pneumonia in 3/38 children (7.89%) (**Table 3**).

Serum levels of calcium and VD3

A serum calcium determination was performed in patients, which was normal for their age, with an average of 10.10 mg/dl (95% CI 9.99–10.22 mg/dl) (**Table 3**).

The mean vitamin D level was 38.72 ng/ml (SD 8.17). After three dosages of VD3, the average concentration increased to 49.00 ng/ml (SD 9.82). Seven patients (18.42%) had insufficient levels (21–29 ng/ml) with an average serum basal level of 26.4 ng/ml (SD 2.57), which increased to 36.28 ng/ml (5.84) after administration of three doses of VD3. Thirty-one patients (81.57%) had sufficient levels with an average serum basal level of 41.50 ng/ml (SD 6.13), which increased after the administration of VD3 to 51.88 ng/ml (SD 8.11) (**Figure 1**).

Regarding VD3 serum levels and nutritional status, patients with ponderal deficit presented an average of 33.76 ng/ml (SD 6.75). Two-fifths of these patients (40%) had insuffiency baseline status of VD3 serum levels and 3/5 (60%) had

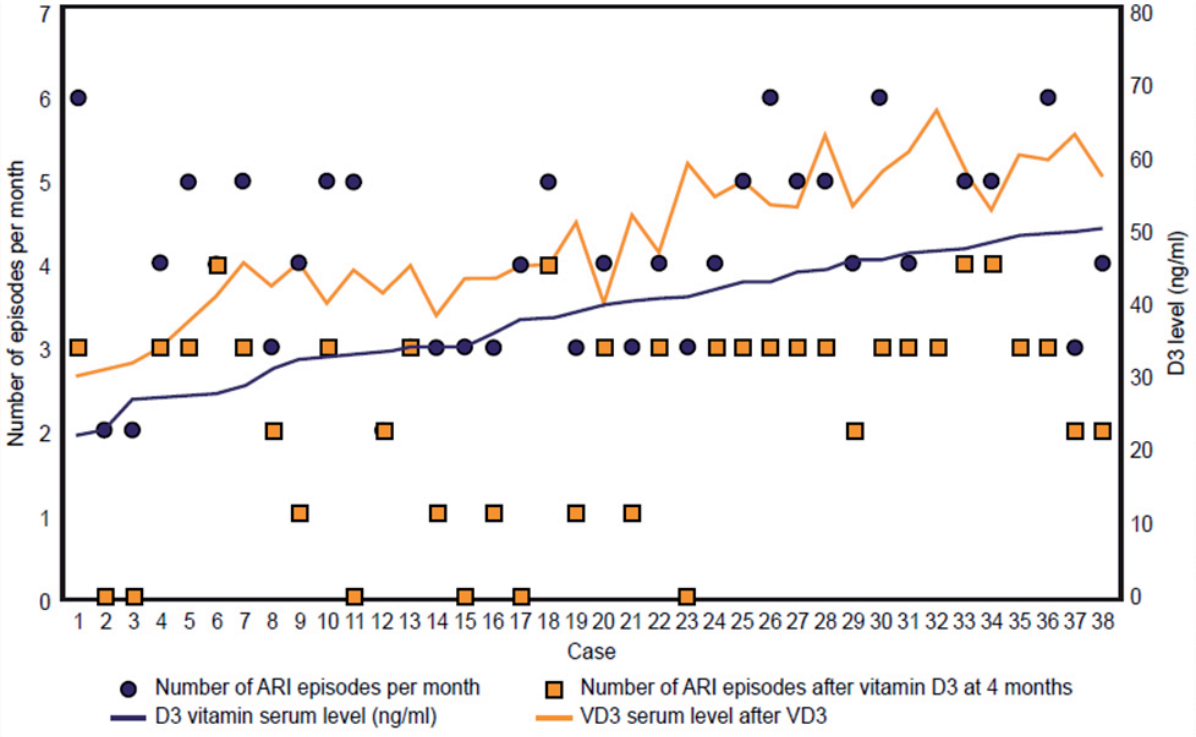

Figure 1. ARI episodes before and after VD3 supplementation. The Acute Respiratory Infection episode number before VDR (blue points) decreased (yellow squares) with increasing VD3 basal levels (blue line) after VD3 administration (yellow line)

a suffiency status. Patients with normal nutritional status had an average VD 3 baseline of 41.07 ng/ml (SD 5.97). A total of 5/30 patients in a normal nutrition state (16.67%) presented an insufficiency baseline status of VD3 levels, and 25/30 (83.33%) in a sufficiency status. In overweight patients, the average VD3 levels were 41.5 ng/ml (SD 9.0), all of them in a sufficiency baseline status of VD3 levels. Although, patients with weight deficit presented lower average baseline serum levels. In general, there was no evidence of significant difference regarding patients with adequate nutritional status and those who were overweight (p = 0.293).

Results of VD3 administration

We observed the number of ARI episodes, the times that the patients were taken to the emergency room and were hospitalized for this cause, before and after administering VD3.

We found that the average number of ARI clinical events in the general studied population prior to VD3 administration was 4.02 events per month (95% CI 3.64–4.40). The number of ARI episodes was reduced as the monthly doses were administered. The reduced number of episodes at the end of the three cycles was 2.23 times per month (95% CI 1.81–2.65; p = 0.0023) (**Table 4**).

In general, the average number of emergency room visits during three months prior to VD3 administration was 2.15 (95% CI 1.77–2.53). After three months of treatment, the average number of emergency room visits decreased to 0.52 (95% CI 0.32–0.72; p = 0.018).

Within the number of hospitalization events during the three months prior to VD3 administration, just once during this period, twelve patients (31.58%) required hospitalization, and two (5.26%) required hospitalization twice. After the administration of three VD3 doses, only one patient (2.63%) required hospitalization (**Table 1**).

VD3 Administration and ARI type

The average number of upper tract ARI episodes in three months of observation prior to administration of VD3 was 3.93 (95% CI 3.50–4.36). These patients were taken to the emergency room an average of 2.06 times (95% CI 1.63–

Table 4. Events Included Consultations for Emergencies and Hospitalization Before and After VD3 Administration

	Total	Basal Level		P Value
		Sufficient VD3	Insufficient VD3	
ARI average episodes (DE) (95% CI)				
Event/month before VD3 administration	4.02 (3.64–4.40)	4.03 (3.63–4.42)	4 (2.58–5.41)	0.0870
In ARI upper tract	3.93 (3.50–4.36)	3.96 (3.51–4.41)	3.8 (2.1–5.5)	
In ARI lower tract	4.50 (3.62–5.37)	4.4 (3.2–5.5)	2 (1.5–2.5)	
Decreased events after VD3 supply	2.23 (1.81–2.65)	2.22 (1.77–2.67)	2.28 (1.43–3.13)	0.0230
After first dosage	0.42 (0.23–0.60)			0.0010
After second dosage	0.47 (0.30–0.64)			0.0001
After third dosage	1.44 (1.17–1.71)			0.0032
For ARI upper tract	2.30 (1.93–2.75)	2.38 (1.97–2.79)	2.16 (1.35–2.97)	
For ARI lower tract	1.66 (0.28–3.629)	1.4 (1.02–3.82)	2 (1.5–2.5)	
Attendances to emergencies during 3 months				
Before VD3 administration				
Average (95% CI)	2.15 (1.77–2.53)	2.12 (1.70–2.55)	2.28 (1.43–3.13)	0.5825
For ARI upper tract	2.06 (1.63–2.49)	2.03 (1.54–2.52)	2.16 (1.93–3.39)	
For ARI lower tract	2.66 (1.80–3.52)	2.60 (1.48–3.71)	3.00 (2.5–3.5)	
After VD3 administration				
Average (95% CI)	0.52 (0.37–0.72)	0.38 (0.20–0.56)	1.14 (0.61–1.67)	0.0180
For ARI upper tract	0.59 (0.37–0.81)	0.45 (0.25–0.66)	1.16 (1.37–1.95)	
For ARI lower tract	0.16 (0.26–0.59)	0 (0)	1.10 (0.97–1.20)	
Hospitalization average (95% CI)				
Internment before VD3 administration	0.421 (0.22–0.61)	0.48 (0.25–0.71)	0.14 (0.1–0.43)	0.3340
Internment after VD3 administration	0.026 (0.02–0.03)	0.032 (0.030–0.097)	0 (0)	0.0368

The table shows the reduction in the number of events, attendance to emergency and hospitalizations after VD3 administration.
Abbreviations: VD3, vitamin D3; ARI, acute respiratory infection.

2.49). The number of episodes per month was reduced by 2.3 times the initial average (95% CI 1.92–2.75) with the VD3 administration, and the average number of visits to the emergency room decreased to 0.59 visits (95% CI 0.37–0.81).

For lower ARI respiratory tract, the average number of episodes per month prior to VD3 administration was 4.5 (95% CI 3.62–5.37), and the number of visits to the emergency room was 2.66 (95% CI 1.80–3.52). After VD3 administration, the average number of ARI episodes was reduced to 1.66 (95% CI 0.28–3.629), and the average number of emergency room visits were reduced to 0.16 (95% CI 0.26–0.59) (**Table 4**).

VD3 Administration and VD3 basal levels

The average number of ARI episodes per month found in patients with sufficiency baseline levels did not show significant differences compared to those with insufficiency levels (4.03; 95% CI 3.63–4.42 vs 4: 95% CI 2.58–5.41, p = 0.087). After administering three VD3 doses, a reduction in episodes was observed for both sufficiency and insufficiency patients (average: 2.22 times; 95% CI 1.77–2.67 and 2.28 times; 95% CI 1.43–3.13, respectively p = 0.047).

Patients with sufficiency and insufficiency were taken to the emergency room at least twice in the three months prior to VD3 administration (average 2.12; 95% CI 1.70–2.55 and 2.28; 95% CI 1.43–3.13 times, respectively; p = 0.5825). These episodes had a significant reduction after VD3 administration (average 0.38; 95% CI 0.20–0.56 and 1.14; 95% CI 0.51–1.60 times, respectively; p = 0.0180).

Of 22/38 patients (57.89%) with a history of hospitalization prior to VD3 administration, 14/22 (36.84%) were hospitalized for bronchiolitis, and 8/22 (21.05%) for CAP. After VD3 administration, only 1/38 (2.63%) was hospitalized (**Table 3**).

Three patients (7.89%) aged between 13 and 60 months, suffered nausea as a side effect to VD3. The other participants had no deleterious effects.

Discussion

In this study, 38 patients of both genders, under age 5 (25.81 ± 17.50 months), in whom an average VD3 baseline value was found to be 38.72 ng/ml (95% CI 36.03–41.40 ng/ml) with 18.42% insufficiency levels, were included. Insufficiency and deficiency status have usually been related to a deficit in intake, as might be expected to occur in patients with nutritional deficits [35–37].

However, no significant difference was found between VD3 baseline levels and nutritional status (p = 0.293), in patients from this survey.

Colombia has one of the highest solar radiation levels in the world due to its tropical location. Cartagena de Indias is located north of the equator (10º 25' 30" north latitude and 75º 32' 25" west longitude), with no seasonal variation. Despite this, in Colombia according to the results of the 2015 National Nutritional Survey, in a group of children aged 1 to 4 years, the total prevalence of vitamin D insufficiency was 35.2% and deficiency was 31.4%.

In a study carried out on 360 eutrophic children under age 10 in a similar Colombian Caribean region, an average value for 25-hydroxyvitamin D of 32.23 ± 8.25 ng/ml was found; 46.38% had levels considered insufficient (<30 ng/ml) and 3.05% showed deficiency (<20 ng/ml) [38]. In Uganda, an analysis was carried out on children between 6–24 months of age, in which no significant differences in VD3 levels and nutritional status were found on patients [39].

Some studies have shown that vitamin D has immunomodulator properties associated with protective effects against infectious diseases, including ARI, and has been proposed as a possible protective measure for these pathologies in pediatrics [30, 40–42]. VD3 benefits have been described in reducing episodes of pharyngotonsillitis [43], nasopharyngitis [44], otitis media, and lower respiratory tract episodes such as bronchiolitis and pneumonia [45]. In study patients, was found that after VD3 administration a reduction in the number of ARI episodes per month ($\overline{X}$ reduced episodes = 2.23 times 95% CI 1.81–2.65; p = 0.0230), visits to the emergency room ($\overline{X}$ = 0.52 consultations/month 95% CI 0.37–0.72; p = 0.0180), and the need to be hospitalized was observed. Taking into account that 57.89% of them were hospitalized for bronchiolitis and pneumonia, and that 5.26% needed to be hospitalized at least twice, prior to VD3 administration.

There is no consensus on needed levels for VD3 functions on the immune system. Although it is estimated that at least between 20 to 50 ng/

ml levels are necessary to achieve an immunomodulator effect [30]. In participants of this study, a VD3 bolus dose of 50,000 units was orally administered per month for 3 months, observing an increase in VD3 serum levels by an average of 49 ng/ml, with a decrease in ARI episodes, emergency room visits, and hospitalization.

In an analysis of 25 clinical trials (11,321 participants aged from 0 to 95 years) conducted in 14 countries, in which VD3 was orally administered, was found that seven studies administered VD3 in monthly boluses for three months, three studies performed it weekly, twelve studies performed it daily, and three more studies performed a daily dose and a combination of bolus. A redution of ARI risk in participants (adjusted OR 0.88; 95% CI 0.81–0.96 p for heterogeneity < 0.001) was found. In subgroups analysis, a protective effect in those who received bolus and daily doses (adjusted OR 0.81, 0.72–0.91) was found, but not in those who received one or more boluses (OR 0.97, 0.86–1.10; p for interaction = 0.05). Serious adverse effects with VD3 administration (adjusted OR 0.98, 0.80–1.20), were not found [42]. In patients described in our study, important secondary effects after VD3 administration, were not observed.

A descriptive study was carried out, in which no associations can be confirmed between exogenous VD3 administration and its influence on the favorable response in the reduction of the number of ARI episodes, visits to the emergency room, and hospitalization in children under age five. The described findings invite us to perform association tests that can sustain this relation.

Conclusions

Vitamin D3 administration could have a benefit in reducing the number of ARI episodes, emergency room visits, and hospital admissions in children under age five, although the supplementation régimen has not been defined yet. Clinical trials are required to determine this potential benefit.

Acknowledgements

To the National Police of Colombia, the EuroEtika Laboratory for the supply of the Histotal® product, To UNIMOL research group of the University of Cartagena (Colombia), and to Colciencias in agreement with Colfuturo (Call No. 727 of 2015).

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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