Vitamin A and D deficiencies in the prognosis of respiratory tract infections: A systematic review with perspectives for COVID-19 and a critical analysis on supplementation

Vitamin A and D deficiencies: Perspectives for COVID-19

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ABSTRACT

OBJECTIVE: Considering the rapid spread of COVID-19, the scientific community has been looking for ways to recognize factors that may interfere with the outcome of viral infection. Despite the lack of studies with the new coronavirus, it is known that adequate serum levels of micronutrients are essential for the organic response to infectious diseases. Thus, we aim to review the effects of vitamin A, D, iron, zinc, or folate deficiency on the prognosis of patients with respiratory infections with manifestations similar to COVID-19 and discuss about supplementation of the nutrients analyzed in this review. **METHODS**: The search was conducted in the databases PubMed, Lilacs, and SciELO, including observational studies published between 2010-2020, with results for individuals with respiratory tract infections with manifestations similar to COVID-19. **RESULTS**: Six articles met the inclusion criteria, all of which were related to deficiencies of vitamins A and D. In general, vitamin A deficiency was associated with cough, fever, and greater total respiratory resistance. Regarding vitamin D, the lack of this nutrient led to higher rates of ICU admission, the need for mechanical ventilation, and mortality. Evidence linking specific relationships between nutritional deficiencies and COVID-19 remain lacking due to the small number of studies and heterogeneities in population subgroups. **CONCLUSION**: In conclusion, deficiencies of vitamins A and D seem to negatively affect the prognosis of respiratory tract infections. Supplementation of these nutrients for prevention or treatment of patients diagnosed with COVID-19 should respect serum levels, nutritional status and housing conditions (e.g.,endemic location) of individuals.

KEYWORDS: Micronutrients; vitamin A; vitamin D; coronavirus; respiratory tract infections.

Introduction

Coronavirus (COVID-19) is a viral respiratory illness caused by the new coronavirus (2019-nCoV) that emerged in December 2019 in the city of Wuhan/China [1]. The rapid geographical spread of the new coronavirus has represented a major challenge for public health [2]. According to the World Health Organization (WHO) report [2], until April 30, 2020, the world pandemic resulted in 3.090.445 confirmed cases and more than 217 thousand deaths resulting from clinical manifestations secondary to infection (fever, dry cough, and shortness of breath) [3,4].

Possible risk factors that affect the disease prognosis in patients infected with the new coronavirus include advanced age, presence of chronic non-communicable diseases, such as hypertension, diabetes mellitus, and cardiovascular diseases [5,6], as well as immune dysregulation [7].

The importance of adequate nutritional status to modulate the immune response and decrease the risk of infections is well established in the literature [8,9]. Micronutrients such as vitamin A, D, iron, zinc, and folate, are highlighted for their participation in several stages of the immune response, including differentiation, proliferation and functioning of innate immune cells; regulation of cytokine; and production/development of antibodies [8].

Considering the lack of scientific evidence regarding the role of nutritional deficiencies in the prognosis of viral infections and, given the current global pandemic scenario of COVID-19, the present study aimed to assess, based on the literature, the effects of deficiency of vitamin A, D, iron, zinc or folate in the prognosis of patients with respiratory infections with manifestations similar to COVID-19 and discuss about supplementation of the nutrients included for qualitative analysis in this review.

Methods

Guidelines

The study design and conduct of this systematic review comprised the recommendations of the Preferred Reporting Items for Systematic Reviews (PRISMA) [10] guidelines and the research protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) [11], under registration number CRD42020178982.

Bibliographic search strategy

The methodological procedure was carried out from March to 30 April 2020, based on the following guiding question, elaborated according to the acronym PECO [12]: "Deficiency of vitamin A, D, iron, zinc or folate in individuals with respiratory infections with manifestations similar to COVID-19 leads to a worse prognosis when compared to those without deficiency?".

The electronic search was performed in the databases: Publisher Medline (PubMed), Latin American and Caribbean Health Sciences Literature Resource (LILACS) and Scientific Electronic Library Online (SciELO). For the search strategy, the following descriptors were used: "Nutritional Deficiency", "Vitamin A", "Vitamin D", "Zinc", "Iron", "Anemia", "Folate", "Folic Acid", "Respiratory Tract Infections", "Influenza", and "Coronavirus". The descriptors were identified in the Medical Subject Headings (Mesh), available at the U.S. National Library of Medicine (http://www.nlm.nih.gov/mesh/), and in the list of Health Sciences Descriptors (http://decs.bvs.br).

The search algorithm for PubMed was: (("malnutrition"[MeSH Terms] OR "malnutrition"[All Fields] OR ("nutritional"[All Fields] AND "deficiency"[All Fields]) OR "nutritional deficiency"[All Fields]) AND ("vitamin a"[MeSH Terms] OR "vitamin a"[All Fields])) AND ("respiratory tract infections"[MeSH Terms] OR ("respiratory"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "respiratory tract infections"[All Fields]). The keywords were changed to provide the inclusion of articles with the other micronutrients and infectious conditions (influenza or coronavirus).

Eligibility criteria

The articles selection criteria included original observational studies, carried out with respiratory infected individuals manifesting similar COVID-19 symptons, published in the last 10 years (between 2010 and 2020), in English, Spanish or Portuguese. The similarity of manifestations of the respiratory infections included in this review with the symptoms of COVID-19 was assessed based on the Epidemiological Bulletin on 2019-nCoV [13], which refers to a broad common clinical spectrum between COVID-19 and other colds, with manifestations ranging from coughing, fever, and shortness of breath to severe pneumonia.

Studies as reviews, letters to the editor, theses, and dissertations addressing bacterial infections like tuberculosis, carried out with experimental models, and whose analytical methodology was the assessment of the association between the infection leading to nutritional deficiency were excluded from the present review. To increase the sensitivity of the search for studies related to iron deficiency, the term "anemia" was included as a descriptor, however, researches that identified anemia exclusively by assessing hematocrit and hemoglobin, and did not evaluate iron status by ferritin and transferrin receptor [14,15], were not considered eligible for the study.

Study screening and inclusion

The articles screening followed three stages: reading the title, reading the abstract, and reading full-text articles. After reading the titles and abstracts, the full texts were read to identify those who met the inclusion criteria, according to the pre-established protocol. The authors independently evaluated the articles and, later, they were gathered for confrontation and confirmation of the investigated data to reduce bias and heterogeneity in the analyzes.

Quality assessment of articles

The articles included in this review received scores from 0 to 22 points, according to the initiative Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [16].

Data extraction

Data extraction was performed in Microsoft Excel 2016 version, using a protocol prepared by the researchers, containing the following data: title of the article, author, place and year of publication, objective and type of study, sample size, characteristics of the study population, diagnosis/clinical manifestation of the infection, the prevalence of nutritional deficiency, and clinical outcomes associated with the deficiency.

Results

Screening and characteristics of included studies

The search for articles resulted in the identification of 1,691 articles corresponding to the respective surveyed micronutrients. Of these, we excluded 29 because they were duplicated. Among the remaining 1,662, after applying the eligibility criteria based on the information provided in the titles and abstracts 1,615 were eliminated. A total of 47 articles were read in full and, in the final stage, 6 studies were considered eligible for this review (Figure 1).

According to STROBE, the median quality of the articles was 17.7 (Interquartile Range=15.6-18.8), with scores ranging from 15.6 to 20 points. All studies included met percentages higher than 50% of this indicator (Chart 1).

The selected studies were published between 2012 and 2018, involving participants from Europe [17], South America [18–20], North America [21], and Asia [22] (Chart 1), with a total of 4,352 individuals (3,388 children and 964 adults and elderlies) of both sexes, with diagnosed community-acquired pneumonia [18,22], acute upper respiratory tract infections [20] or acute lower respiratory infections [17,21], and predicting clinical symptoms of viral infections, such as cough with fever [19].

Four studies were carried out at a hospital [17,18,21,22], one in a specialized clinic, [20] and one in primary schools [19] (Chart 1). The included studies were two cross-sectional studies [18,20] two prospectives [17,19] one population-based observational study [21] and one with retrospective design [22].

Regarding the nutrients considered in the search stage, we found articles that met the inclusion criteria for vitamin A [19–21] and vitamin D [17,18,21,22].

Vitamin A

Vitamin A deficiency in non-hospitalized children between 0 and 12 years old with respiratory tract infections, reached a prevalence of 12-46% [19–21], and a severe deficit reached 1.2-3.9% of the participants [19,20]. Serum retinol levels were inversely related to cough with fever ($p=0.05$) [19], and to an increase in total respiratory resistance in individuals without wheezing ($p<0.05$) [20]. Children with vitamin deficiency were more likely admitted to the ICU ($p<0.05$), an association that lost significance when adjusted analyzes were conducted [21], and those with severe deficit were 2.4-fold more likely to present cough with fever. An increase of 10mg/dL of plasma retinol was a protective factor contributing to 10% fewer days of cough with fever ($p<0.001$) and 6% fewer visits to the doctor ($p<0.05$) [19]. Amaral et al. [20] observed that patients with infections without wheezing and with vitamin A deficiency had difficulty recovering of respiratory resistance even after clinical treatment for infection (Chart 2).

Vitamin D

All included studies that assessed the impact of vitamin D, regardless of age, were conducted with hospitalized patients. In children, the prevalence of vitamin D deficiency ranged from 12% to 85% [17,21] and was positively associated with a higher risk of severe signs of breathing difficulties (OR:5.065; 95%CI:1.998;12.842; $p<0.001$) [17]. Children with vitamin D levels below 20ng/mL presented 117% more chances of using oxygen support and 217% more chances of needing respiratory support [17]. In addition, Hurwitz et al. [21] showed that vitamin D deficit in the pediatric group contributed to greater chances of ICU admission (OR: 3.29; 95%CI: 1.20;9.02; $p<0.05$) and mechanical ventilation (OR: 11.2; 95%CI: 2.27;55.25; $p<0.001$). In hospitalized adults and elderlies, vitamin D deficiency was prevalent in 80 to 85% of the sample [18,22]. Brance et al. [18] found no association between the disease symptoms and levels of respiratory infection. Kim et al. [22] observed that, after statistical adjustments, there was an increased risk for mortality in 28 days in the group with 25-hydroxyvitamin D (25(OH)D) deficiency (OR: 3.31; 95%CI: 1.17– 9.39; $p<0.05$) (Chart 2).

Discussion

Vitamin A and D deficiencies and outcomes of respiratory infections

Evidence suggests that micronutrient deficiency is one of the main etiological factors involved in the global burden of diseases, where deficiencies in vitamins A, D, iron, zinc, and folate stand out as important public health problems, especially in developing countries [23–25]. Such epidemiological scenario led to the choice of these micronutrients to be addressed in the present review.

During the search stages, investigations involving analysis of iron, zinc, and folate did not meet the necessary criteria for inclusion in this study, thus the results were limited to findings corresponding to vitamin A and D, showing that the deficiency of these nutrients appears to be a predictor of clinical complications in the course of the assessed respiratory infections.

Indeed, studies confirm that maintaining nutritional status is associated with immune integrity [26–28] and International Society for Immunonutrition reinforces the importance of eating diversified and balanced foods, rich in antioxidant nutrients, aiming to promote healthy eating practices in times of pandemic [29].

Among the nutrients with such characteristics, vitamin A is part of the intervention strategies, since it reduces the susceptibility to pathogens in the mucosal epithelium of digestive and respiratory tract [8], playing an essential role in the regulation of growth, differentiation and gene expression of airway epithelial cells [30].

The described functions may in part explain the results related to vitamin A in the present study, which demonstrated that the deficiency of this nutrient in children was associated with outcomes such as cough with fever, a greater number of visits to the doctor, greater total respiratory resistance, and less response to clinical treatment of acute upper respiratory infection.

Supporting this tendency Qi et al. [31] in a survey with 684 Chinese children (age range 5 months to 12 years old), observed that vitamin A deficiency (retinol<0.2mg/L) was a risk factor for the development of acute respiratory tract infection (p<0.05). It is worth noting the possibility of non-causal effects in these findings, as it is known that vitamin A concentrations may decrease in the presence of infectious conditions due to the acute phase response [32].

Barbosa et al. [33] when following Brazilian children with and without pneumonia, found that serum retinol levels were statistically lower during the inflammatory process than after recovery (1.11±0.43 *vs.* 1.38±0.30μmol/L; p<0.05). The authors attributed this finding due to the acute phase response associated with reduced mobilization of hepatic nutrient reserves, as well as the increased need for retinol secondary to the improved activity of immune cells in pneumonia.

Although the results related to vitamin D are heterogeneous, it is known that vitamin D deficiency has been a common nutritional disorder in patients diagnosed with respiratory tract infections [34,35]. Inamo et al (2011) [36], in their hospital-based retrospective case study, observed that Japanese children (mean age 14.03±11.43 months) with bronchiolitis or pneumonia who had vitamin D deficiency (<10ng/mL) were the ones who most needed oxygen and/or ventilation support (p<0.01).

On the other hand, Xu et al (2016) [37], when evaluating 2,694 children and adults in Hong Kong, did not find an association between the lowest serum concentrations of 25(OH)D (<50nmol/l) and the risk of infections by influenza virus (RR: 1.15; 95%CI: 0.73;1.83; p=0.55) after adjusting for age, sex, chronic disease, and vaccination history. However, the authors observed an association with the incidence of influenza-like symptoms (presence of fever ≥37.8ºC and cough or sore throat) (RR: 1.70; 95%CI: 1.14;2.51; p=0.01).

According to a case-control study conducted by Mamani et al (2017) [35] with 149 adults diagnosed with community-acquired pneumonia, the risk of pneumonia among individuals with deficient levels of vitamin D (<10ng/mL) was 3.69-fold (95%CI: 1.46;9.31) greater than those with sufficient levels (>20ng/mL) ($p<0.01$).

The biochemical profile of vitamin D in patients diagnosed with COVID-19 is still unknown. Thus, it is suggested that determining vitamin D levels in baseline blood samples may be a way of investigating the impact of vitamin D levels on the prognosis of COVID-19 and justifying the possible therapeutic action of vitamin D in the treatment of 2019-nCoV.

Perspectives on Vitamin D and A supplementation

Zhang and Liu [38], in a recent publication, discuss possible nutritional interventions for 2019-nCoV and claim that vitamin A can be a promising strategy for the treatment and the prevention of lung infections, however, they do not suggest dosages or protocol for supplementation.

Cochrane review published by Chen et al. [39] demonstrated unexpected effects for megadose supplementation (100.000-206.000 IU/day) or low doses (5.000 IU/day or 8.333-10.000 IU/week or 20.000-45.000 IU every two months) of vitamin A in children from 0 to 7 years old. The results showed no effect and some of the studies revealed exacerbation of clinical symptoms (cough with fever, tachypnea and higher incidence of acute respiratory infections) in children who used vitamin supplementation. The authors report that beneficial effects may be more prominent in children with pre-existing malnutrition, concluding that low doses of vitamin A leads to fewer side effects and shows similar benefits to those found in megadose supplementation.

In a research conducted by Mawson [30], an extensive consideration about vitamin A supplementation in Influenza infection was available, verifying that supplemental vitamin A seems to induce Influenza-like symptoms, a hypothesis formulated given the increase in respiratory symptoms reported in the studies analyzed by the review. Nevertheless, the author concludes that retinoids can act both to fight infection and to induce symptoms, with the serum vitamin D concentration being a critical factor determining the action of retinoids (previous vitamin D deficiency seems to determine greater toxicity of endogenous retinoids).

Clinical trials on vitamin D supplementation that assessed the prevention of respiratory infections and/or the severity of the disease indicated heterogeneous results [40-44], which can be explained by the varying doses of vitamin D (400 to 100.000 IU per day, week and/or single dose), and protocol duration (5 days to 8 months). However, a meta-analysis including 25 randomized controlled trials and totaling 10,933 participants showed a protective effect of vitamin D supplementation against acute respiratory tract infection [45].

A recent literature review [46], discussing the evidence on vitamin D supplementation during COVID-19 pandemic, proposed that, in the hospital setting, patients and staff should take vitamin D supplements to increase 25(OH)D for at least 40–50ng/mL (100–125nmol/L). To achieve these concentrations, the authors suggested taking 10,000IU/d for a month and then decrease to 5,000IU/d for maintenance. However, it is stated that "The hypothesis that vitamin D supplementation can reduce the risk of influenza and COVID-19 incidence and death should be investigated in trials to determine the appropriate doses, serum 25(OH)D concentrations, and the presence of any safety issues."

Conclusions

In summary, deficiencies of vitamins A and D may negatively affect the prognosis of respiratory tract infections and supplementation of these nutrients for prevention or treatment of patients diagnosed with COVID-19 should respect serum levels, nutritional status and endemic areas.

Some limitations must be considered when interpreting the presented data, such as the inclusion of observational studies, interfering in some causality relationships; the heterogeneity of the selected studies made it impossible to calculate a summary measure (meta-analysis), however, the use of strategies such as checking the quality of articles can help to control this bias; and the absence of original studies with a nutritional approach in patients with COVID-19 restricted inferential aspects.

It is worth emphasizing the importance of recognizing endemic nutritional deficiencies in communities dealing with the 2019-nCoV pandemic, so that specialized measures can be taken to control deficits in serum vitamins and minerals and, consequently, control the prognosis of infectious conditions.

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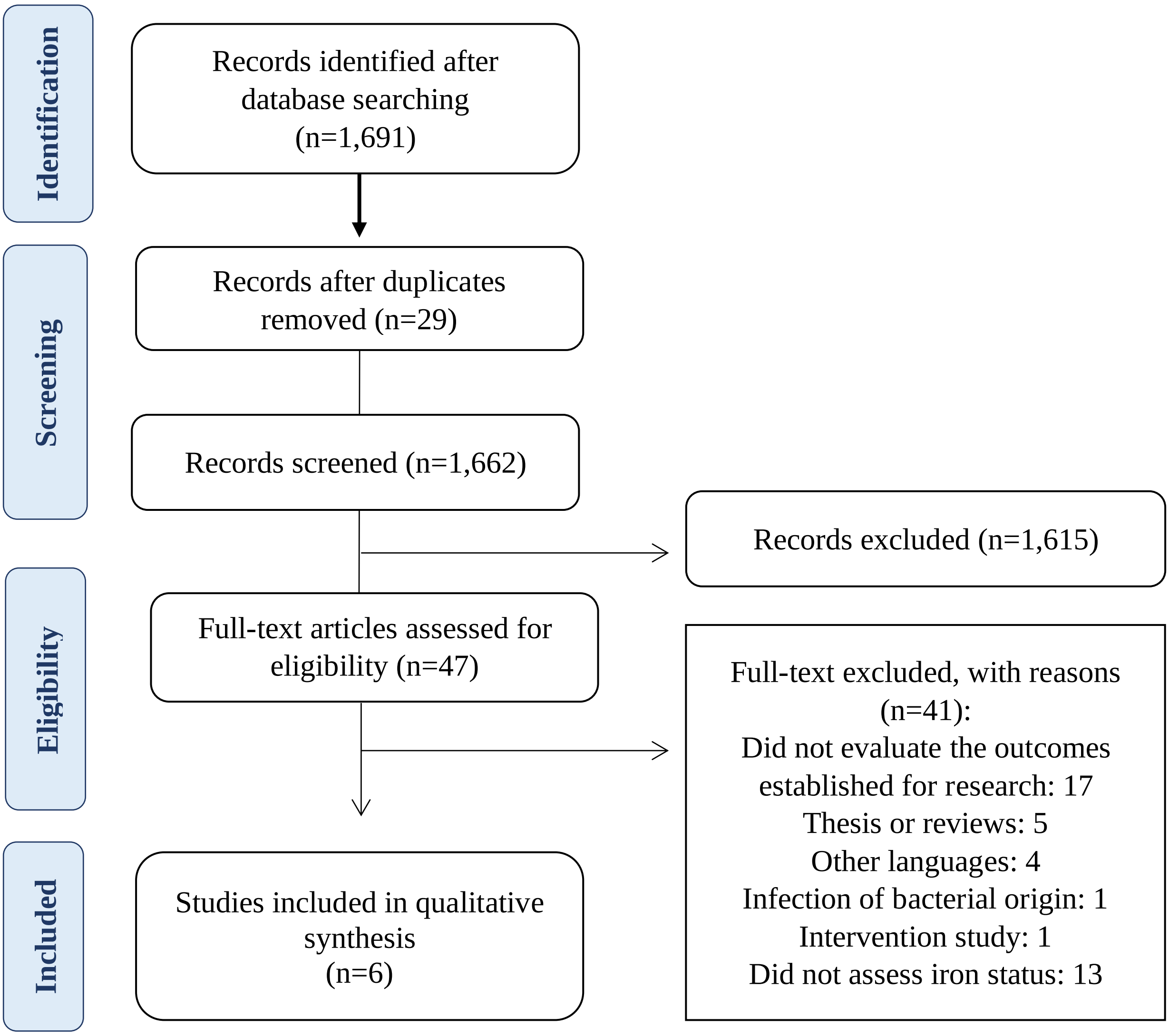

Figure 1. PRISMA Flowchart for inclusion of studies in the systematic review.

Chart 1. General characteristics and quality score of selected articles included in the systematic review.

Reference	Location, year	Study design	Population (n)	Population characteristics	Score*
Brance et al.	Argentina, 2018	Cross-Sectional	167 hospitalized adults	Age range: 18-96 years old ($\bar{x}$±SD=57,4±19,6 years) 41% M; 59% F	15.6
Hurwitz et al.	USA, 2017	Population-based observational study	90 hospitalized children	Median age: 19 months (IQR=10-30) 52% M; 48% F	15.6
Cebey-López et al.	Spain, 2016	Prospective hospital-based	347 hospitalized children	Median age: 8.4 months (IQR=2.6-21.1) 62.1% M; 37.9% F	18.5
Kim et al.	South Korea, 2015	Retrospective observational	797 hospitalized adults and elderlies	Age range: 18-96 years old ($\bar{x}$±SD=68.1±14.6 years) 66% M; 34% F	17.5
Thornton et al.	Colombia, 2014	School-based prospective cohort	2,774 children from primary schools in public schools	Age range: 5-12 years old ($\bar{x}$±SD=8.7±1.8 years) 50.5% M; 49.5% F	20.0
Amaral et al.	Brazil, 2012	Cross-Sectional	177 children recruited at a pediatric clinic	Age range: 4-6 years old ($\bar{x}$±SD=59±1.58 months) 50.3% M; 49.7% F	17.9

$\bar{x}$±SD= Mean ± Standard Deviation; IQR= Interquartile Range.
M= Male; F= Female; USA= United States of America.
*Evaluation of the quality of articles, according to the initiative Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Chart 2. Infection/symptoms related to respiratory infection, prevalence of nutritional deficiency and clinical outcomes associated with nutritional deficiency reported in the included studies in the systematic review.

Included studies that assessed the prognosis of respiratory infections with manifestations similar to COVID-19 in vitamin A deficiency				
Author, year	**Infection/ Symptoms**	**Method for diagnosis of deficiency**	**Deficiency (%)**	**Outcomes associated with nutritional deficiency**
Hurwitz et al, 2017	Lower respiratory tract infection with detection of respiratory syncytial virus (RSV) and/or human metapneumovirus (HMPV)	Retinol binding protein (deficiency <15ng/mL or <7μmol/L)	46%	In the univariate analysis, patients with vitamin A deficiency had higher rates of ICU admission (27% vs. 8%; p=0.02). In the inverse probability-weighted estimation model, vitamin A lost its association with the analyzed outcomes (ICU admission (p=0.198), need for mechanical ventilation (p=0.437), and length of hospital stay (p=0.449)).
Thornton et al, 2014	Cough with fever (a predictor of Influenza infection, and a variety of viral and bacterial infections)	Serum retinol (deficiency=10-19.9μg/dL and severe deficiency <10.0 μg/dL)	Deficiency =12.3% Severe deficiency =1.2%	Vitamin A concentrations were inversely related to cough with fever (p=0.05). Children with severe vitamin A deficiency had 2.4-fold more days of cough with fever (IRR: 2.36; 95%CI: 1.30;4.31). After adjusting for explanatory variables (gender, age, educational level and maternal parity, household food insecurity, and hemoglobin), each 10mg/dL of plasma retinol contributed for 10% fewer days of cough with fever (p<0.001) and 6% fewer visits to the doctor (p=0.01).
Amaral et al, 2012	Acute upper respiratory tract infection and Acute upper respiratory tract infection with wheezing	Serum retinol (deficiency=10-20μg/dL and severe deficiency <10μg/dL) and Modified Relative Dose Response - MRDR (>0.060)	Deficiency=24.2% Severe deficiency=3.9% Deficiency assessed by MRDR=26.8%	There was a significant inverse linear relationship between MRDR or retinol and decreased total respiratory resistance for individuals in the infection group without wheezing (the lower the MRDR, the greater the deficiency of vitamin A stores, and the greater the total respiratory resistance (p=0.015); and the lower the retinol, the greater the total respiratory resistance (p=0.02)). Patients with the infection without wheezing, and with vitamin A deficiency (assessed by MRDR) did not show a reduction in total respiratory resistance after clinical treatment for the infection (Mean total respiratory resistance in infection ($\bar{x}$±SD=1.14±0.22) vs. recovery ($\bar{x}$±SD=1.15±0.21); p=0.565).

IRR= Incidence Rate Ratios; 95%CI= 95% Confidence Interval; $\bar{x}$±SD= Mean ± Standard Deviation. *p-value indicative of statistical significance when <0,05.
MRDR= Modified Relative Dose Response; ICU = Intensive Care Unit.

Chart 2 (Continuation). Infection/symptoms related to respiratory infection, prevalence of nutritional deficiency and clinical outcomes associated with a nutritional deficiency reported in the included studies in the systematic review.

Included studies that evaluated the prognosis of respiratory infections with manifestations similar to COVID-19 in vitamin D deficiency				
Author, year	**Infection/ Symptoms**	**Method for diagnosis of deficiency**	**Deficiency (%)**	**Outcomes associated with nutritional deficiency**
Brance et al, 2018	Community-acquired pneumonia	25(OH)D (deficiency <20ng/mL)	85%	There were no significant differences in symptoms (fever, sputum, hypothermia, dyspnoea, chest pain, and length of hospital stay) and in the physical examination of patients hospitalized with pneumonia, findings that occurred regardless of serum levels of 25(OH)D.
Hurwitz et al, 2017	Lower respiratory tract infection with detection of respiratory syncytial virus (RSV) and/or human metapneumovirus (HMPV)	25(OH)D (deficiency <20ng/mL)	12%	Children with vitamin D deficiency admitted to the ICU, had a greater need for mechanical ventilation when compared to those without deficiency in the univariate analysis (27% vs. 4%; p=0.02). The inverse probability-weighted estimation model shows that vitamin D deficiency remained associated with the need for mechanical ventilation (OR: 11.2; 95%CI: 2.27;55.25; p<0.001), demonstrating statistical significance with ICU admission (OR: 3.29; 95%CI: 1.20;9.02; p=0.018).
Cebey-López et al, 2016	Acute lower respiratory tract infection	25(OH)D (deficiency <20ng/mL)	62.8%	Patients with 25(OH)D deficiency had a higher risk of severe signs of respiratory distress (OR: 5.065; 95%CI: 1.998;12.842; p<0.001) than patients with normal values of this nutrient. Children with levels below 20ng/mL showed 117% more chances of using oxygen support and 217% more chances of needing respiratory support.
Kim et al, 2015	Community-acquired pneumonia	25(OH)D (deficiency <20ng/mL)	80.4%	28-day mortality was significantly higher in the group with 25(OH)D deficiency than in the non-deficient group (8.3% vs. 2.6%; p = 0.01). After statistical adjustments, the risk for mortality at 28 days in the 25(OH)D deficient group was OR: 3.31 (95%CI: 1.17;9.39; p=0.03).

OR=Odds Ratio; 95%CI= 95% Confidence Interval; SD=Standard Deviation. *p-value indicative of statistical significance when <0,05.
25(OH)D= 25-hydroxyvitamin D; ICU = Intensive Care Unit.