Breastfeeding and Vitamin D in Preventing Childhood Infections

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Human milk is the best food for infants. Breastfeeding has been associated with a reduced risk of viral and bacterial infections. Breast milk contains the perfect amount of nutrients needed to promote infant growth, except for vitamin D. Vitamin D is crucial for calcium metabolism and bone health, and it also has extra-skeletal actions, involving innate and adaptive immunity. As exclusive breastfeeding is a risk factor for vitamin D deficiency, infants should be supplemented with vitamin D at least during the first year. The promotion of breastfeeding and vitamin D supplementation represents an important objective of public health.

breastfeeding human milk infections vitamin D supplementation COVID-19

1. Breastfeeding and Infections

Breast milk has been described as a complex and highly variable bioactive fluid, with changes in composition depending on the stage of lactation (from colostrum to late lactation), time of day, and maternal nutritional status. Moreover, breast milk is a source of bioactive molecules, bacteria, and immune cells (including macrophages, T cells, stem cells, and lymphocytes) that enhance immune maturation and protect the newborn against infections and inflammation [1]. Indeed, in addition to essential nutrients for early growth and development, human milk contains various immunologic components, such as α-lactalbumin, lactoferrin, lysozyme, and secretory immunoglobulin (Ig) A [2][3]. Colostrum, with its anti-inflammatory and anti-infectious properties, is particularly important during early postnatal life when neonatal adaptive immune system is still immature and ineffective to protect against pathogens [4].

Human milk shows high inter-individual variability, with the most profound changes observed in lipids composition, including long-chain polyunsaturated fatty acids which have showed immune-regulatory properties [5]. While several infant-related factors (i.e., birth weight, gestational age, and infant age) are known to affect nutritive and non-nutritive components of breast milk, there is limited or conflicting evidence regarding the possible role of maternal factors (i.e., maternal lifestyle, obstetric history, and medical conditions), except for mother’s diet that significantly influences milk composition. For example, at present there is inconsistent evidence that maternal atopy/allergy may affect breast milk composition of interleukins, growth factors, pro-inflammatory markers, cytokines, and fatty acids [6][7][8][9][10][11][12][13][14][15][16]. However, it has been reported that human milk growth factors and cytokines levels varied between populations for unknown reasons, and breast milk mediator levels declined at different rates postpartum, suggesting specific biological roles for human milk growth factors and cytokines in early postnatal development [17].

WHO recommended that all mothers should be supported to initiate breastfeeding as soon as possible after birth, within the first hour after delivery [18]. The early onset of breastfeeding is a simple, but effective, intervention to significantly improve neonatal morbidity/mortality outcomes, as reported by a systematic review of 18 studies. Particularly, breastfeeding was associated with lower risks of all-cause neonatal mortality (also among low-birth-weight babies), and infection-related neonatal mortality [19]. Breastfeeding help to restore intestinal microbiota in newborns from cesarean section, in which Bifidobacterium is less represented, with consequent reduction risk of contracting respiratory infections and diarrhea in early childhood [20]. The importance of promoting exclusive breastfeeding has been reinforced by a meta-analysis (13 studies; n = 46,499), finding that infection-related mortality risk in the first 5 months of life was higher in predominantly, partially, and non-breastfed infants compared to the exclusively breastfed ones. Moreover, non-breastfed children aged 6–23 months had higher risk of all-cause and infection-related mortality than children who continued breastfeeding [21]. The sudden protective effect of breastfeeding was reported by a retrospective case–control study, enrolling 140 infants aged <1 month. This research showed that exclusive or predominant breastfeeding, as opposed to formula or partial breastfeeding, significantly reduces the risk of neonatal fever-related hospitalization by over two-fold [22].

A combined action of peer-support groups and International Board-Certified Lactation Consultants is essential to promote breastfeeding support strategies, to enhance maternal empowerment, and to increase the knowledge of the protective effect of human milk against infections [23][24]. Particularly, peer-support for breastfeeding is associated with longer duration of exclusivity. Not surprisingly, breastfeeding promotion for low-birth weight babies in critical care is also cost-effective, being associated with lower costs and greater health benefits for mothers and infants [25]. Exclusive breastfeeding has been associated with risk reduction of gastrointestinal infections in late preterms [26]. The implementation of steps 1–9 of the Baby Friendly Hospital Initiative (BFHI) was associated with a significant reduction in frequency of mild and severe episodes of diarrhea and respiratory infections in infants younger than 6 months in Democratic Republic of Congo. Promoting BFHI steps 1–9 was also associated with a decreased incidence of both health facility and hospitalizations due to diarrhea and respiratory illness [27]. Recently, it has been estimated that failing to comply with WHO recommendations for breastfeeding entails a healthcare system cost of 118 million US dollars annually for the treatment of diarrhea and pneumonia/respiratory disease in Indonesia [28].

Despite early pacifier use being associated with breastfeeding discontinuation, no significant association was found with respiratory infections, even if constant pacifier use was shown to correlate with a slightly higher risk of coughing and wheezing [29].

Several studies evaluated the possible preventive action of natural breastfeeding against infectious diseases in early childhood, but only few extended follow-ups to second and third infancy [30][31][32][33][34][35][36][37][38]. Some studies suggested that the protective effect of human milk was maximum during the first 6–12 months of life, while others found that significant reduction in infections risk lasted up to the age of 2 years or even beyond [30][31][32][37][38]. Conversely, in the cohort study of Tarrant, M. et al. (8327 children followed until 8 years of life) breastfeeding status at 3 months was not associated with hospitalization for infectious diseases beyond 6 months of age [33].

1.1. Breastfeeding and Respiratory Tract Infections

Several studies assessed the association between breastfeeding and the risk of upper and lower respiratory tract infections in childhood, most of which found a significant protective role of human milk, despite different applied methodology and various populations enrolled . Predominant breastfeeding for 3–6 months was associated with a significant reduction in contracting respiratory infections during the first 6 months of life [39]. Similarly, a Spanish cohort study (580 children evaluated from birth to 14 months) confirmed that predominant breastfeeding for 4–6 months was associated with a lower risk of wheezing, low respiratory tract infections, and atopic eczema between 7 and 14 months of life [40].

A systematic review of 13 studies in Asian infants confirmed that breastfeeding compared to infant formula was associated with significantly lower rates of respiratory tract infections and diarrhea in the first year of life [41]. A recent nationally representative survey in Ethiopia (1034 infants aged < 6 months) demonstrated that exclusively breastfed subjects had a significant reduction in the frequency of illness with fever in the last 2 weeks compared to non-exclusively breastfed infants. Particularly, exclusively breastfed babies had lower odds ratio (OR) of having an illness with cough (OR 0.38) and diarrhea (OR 0.33) [42]. This finding agreed with the results of a large USA prospective longitudinal study (6861 children with a follow-up of 4 years) that found an inverse significant association between breastfeeding and the risk of respiratory infections with fever (OR 0.82), otitis media (OR 0.76), and infectious gastroenteritis (OR 0.55) at 3–6 months of life. Breastfeeding within any 3-month period was inversely associated with ear infection, gastroenteritis, conjunctivitis, laryngitis, and tracheitis also at 6–18 months. Finally, exclusive breastfeeding duration was weakly inversely associated with the risk of otitis media up to 48 months of age (OR 0.97). Taken together, these results suggest that breastfeeding can provide a mild protection against infections also after the first 6–12 months of life [34].

A Brazilian ecological study showed that prevalence of both exclusive breastfeeding among children under 6 months and breastfeeding among children 9–12 months-old were associated with a lower risk of hospitalization for pneumonia during the first year of life [43]. A meta-analysis confirmed that pneumonia mortality was higher among non-breastfed compared to exclusively breastfed infants aged < 5 months, and among non-breastfed compared to breastfed infants and young children aged 6–23 months [44]. These results reinforced the importance of promoting exclusive breastfeeding during the first 6 months of life and continuing breastfeeding thereafter.

A recent Indonesian retrospective case–control study found that 7–12 months-old non-breastfed infants had a 14 times higher risk of contracting respiratory infections [45]. Another prospective study evaluated 926 Greek children, recording feeding modalities and infectious episodes (acute respiratory tract infections, acute otitis media, gastroenteritis, urinary tract infections, conjunctivitis, candidiasis) during the first year of life. Children exclusively breastfed for 6 months had fewer infectious episodes (particularly respiratory infection and acute otitis media) and hospital admissions than those who were partially or non-breastfed. On the other hand, partial breastfeeding was not related to any protective effect against infections [46].

The French EDEN mother–child study, a cohort study with 8 years of follow-up, did not demonstrate a significant protective effect of breastfeeding on longitudinal patterns of cold/nasopharyngitis, skin rash, or respiratory symptoms. However, ever-breastfed infants had a significant lower risk of diarrhea in early infancy and bronchitis/bronchiolitis throughout infancy compared with never breastfed infants. Only predominant breastfeeding duration was related to frequent events of bronchitis/bronchiolitis and infrequent events of otitis [35].

In a USA prospective longitudinal study (1281 subjects followed until 6 years of life), children breastfed longer than 9 months had lower risk of past-year ear (OR 0.69), throat (OR 0.68), and sinus (OR 0.47) infections compared with those breastfed less than 3 months [38]. A meta-analysis confirmed that breastfeeding protects against acute otitis media until 2 years of life, and exclusive breastfeeding for the first 6 months was associated with higher risk reduction (43%) [47]. More recently, a Turkish cohort study (411 children evaluated up to 5 years of life) showed that breastfeeding longer than 12 months significantly reduced the risk of acute otitis media and acute gastroenteritis [37].

A large cohort study from UK (4040 children aged 1.00–1.99 years) evaluated the prevalence of frequent colds (>6 episodes), ear infections and croup within the last 12 months, and any episodes of bronchiolitis or pneumonia in relation with breastfeeding duration. This research found limited evidence of a protective effect of breastfeeding against all types of respiratory tract infections during the first 2 years of life, but results suggested that prolonged breastfeeding (>6 months) might protect against bronchiolitis (risk reduction of 28%) [48]. The reasons for this different efficacy of breastfeeding in reducing only bronchiolitis risk are not fully understood; however, another retrospective study (411 infants, age < 1 year) showed that the risk for requiring oxygen therapy to treat respiratory syncytial virus (RSV) bronchiolitis was significantly higher in the artificial-milk-formula-fed group than in the breastfed group [49]. A recent cohort study in Spain (969 infants) showed that any breastfeeding was significantly associated with a lower incidence of bronchiolitis and number of episodes of bronchiolitis in the first year of life, confirming that breastfeeding may represent an effective primary prevention strategy against bronchiolitis [50].

The protective role of breastfeeding against bronchiolitis is particularly relevant during actual coronavirus disease 2019 (COVID-19) pandemic. In 2020, a dramatic reduction in RSV bronchiolitis hospitalization was reported worldwide, coinciding with the spread of SARS-CoV-2 infection [51][52][53]. The most accredited hypothesis to explain this uncommon finding was that the strict adoption of non-pharmaceutical interventions to contain SARS-CoV-2 diffusion (including handwashing and social distancing) also reduced the circulation of other infectious agents, such as RSV [52]. Unfortunately, this reduction was only transient, with subsequent rebound during the fall and winter seasons in 2021–2022 [53][54][55]. For example, a recently published French study reported a delayed RSV epidemic in the period usually corresponding to the end of the epidemic season [56].

Breastfeeding and parent-reported hospitalizations, bronchiolitis and otitis events, and antibiotic use were prospectively collected up to 2 years among 9703 young children from the nationwide Etude Longitudinale Française depuis l'Enfance (ELFE) birth cohort. This research showed that the number of bronchiolitis events was not significantly related to ever breastfeeding or to breastfeeding duration, but predominant breastfeeding duration tended to be negatively related to the risk of frequent bronchiolitis events. Similarly, both any and predominant breastfeeding were not related to frequent otitis events. In contrast, any breastfeeding duration < 3 months was associated with higher risks of hospitalizations from gastrointestinal infections or fever, predominant breastfeeding duration < 1 month was associated with higher risk of a single hospital admission, and ever breastfeeding was associated with lower risk of antibiotic use, confirming a lower risk of infectious morbidity related to breastfeeding duration [57]. However, in another cross-sectional study ever breastfeeding compared with exclusive formula feeding was associated with decreased risk (−36%) of a lower versus upper acute viral respiratory tract infection, suggesting that even if exclusive breastfeeding is the recommended feeding method within the first 6 months, partial breastfeeding may also provide some protection against lower respiratory tract infections [58]. A Danish cohort study confirmed that the risk of hospitalization due to any infection in the first year of life decreased with a longer duration of any breastfeeding. Compared with never or partially breastfed group, exclusive breastfed infants for ≥4 months had a significant reduced risk (−55%) of hospital admissions for any infection for the first 24 to 36 months of life. Considering infection types, every extra month of any breastfeeding lowered the risk of lower respiratory tract and other infections (5% for both). On the contrary, no protective associations were found between breastfeeding and infection symptoms registered at home from ages 12 to 36 months [36]. Similarly, another cohort study found that protection against infections conferred by breastfeeding was limited to the first 12 months of life. Indeed, the higher risk of hospitalization was observed in breastfed children ≤ 6 months compared to ≥12 months (relative risk 1.22), but with similar risks for 6 to 11 months versus ≥12 months. Considering the time of weaning, breast-fed children who received complementary foods at 4 to 6 months of age had similar risk for infection as those receiving complementary foods after 6 months [59]. Conversely, a large cohort study (5322 children) highlighted that breastfeeding for ≥ 6 months was significantly associated with a reduced risk of lower respiratory tract infection (OR 0.71) up to 4 years of age [31], suggesting that breastfeeding effect against respiratory infections may persist beyond the first year of life.

Two other studies confirmed that breastfeeding significantly reduced hospitalization risk due to infections. A Japanese longitudinal study (43,367 children) showed that human milk was associated with reduced risk of hospitalization for respiratory infections (but not diarrhea) during second infancy (between 30 and 42 months of life) [32], and a cohort study in Honk Kong (8327 subjects) found that breastfeeding for >3 months was associated with a lower risk of hospital admission in the first 6 months of life for respiratory infections, gastrointestinal infections, or any infection [33].

Another large cohort study (15,809 infants from the UK Millennium Cohort Study) demonstrated that exclusive breastfeeding was associated with chest infections and diarrhea, but not with ear infections. Particularly, infants exclusively breastfed for <4 months had an increased risk of respiratory infection (risk ratios 1.24–1.28) and diarrhea (risk ratios 1.42–1.66) compared with the pre-2001 WHO policy (starting solids, but not formula, before 6 months, and continuing breastfeeding at 6 months). Moreover, this research found an excess risk of chest infections and diarrhea also among infants exclusively breastfed for 4–6 months, but who stopped breastfeeding by 6 months, highlighting the importance of continuing breastfeeding beyond 6 months of life [60].

Apparently contradictory results come from an Italian case–control study (496 infants aged < 6 months) reporting that exclusive breastfeeding at infant symptom onset was associated with a higher risk of viral respiratory infection

(OR 3.7) confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR). Breastfeeding may represent a proxy for closer contacts of the infant with the mother and, possibly, with other household members. However, in this research a longer breastfeeding period conferred a mild protection against viral respiratory infections (OR 0.98), suggesting that protective role of breastfeeding increases with duration [61]. This research also reinforced the importance of adopting Center for Disease Control and Prevention recommendations for the prevention of viral respiratory infections transmission to infants (symptomatic mothers should thoroughly wash their hands with soap and water before touching the infant and cover their nose and mouth with a tissue when sneezing or coughing in close contact with the infant) [62].

A protective effect of breastfeeding has been reported also against enterovirus infections responsible for hand, foot, and mouth disease. Interestingly, prolonged exclusive breastfeeding reduced the risk of developing fever, possibly due to some anti-inflammatory components of human milk that can reduce the production of pyrogenic substances. Moreover, breastfeeding can reduce infant discomfort conferring emotional support from the intimate contact with mother [30]. Finally, a Brazilian case–control study (267 infants < 6 months) confirmed that children exclusively breastfed and with mothers vaccinated against pertussis during pregnancy were 5 times less likely to develop a pertussis-like illness (OR 0.21) [49].

1.2. Breastfeeding and Gastrointestinal Infections

Some studies assessed the implication of natural breastfeeding on gastrointestinal infections in infancy. Once again, human milk seems protective against diarrheal diseases development and severity as breastfeeding was significantly associated with reduced incidence/risk of acute gastroenteritis [27][20][39][34][40][60][35][37][42][41]. A meta-analysis of 18 studies found that not breastfeeding was associated with an increased risk of diarrhea mortality in comparison to exclusive breastfeeding among infants aged <5 months and to any breastfeeding among children aged 6–23 months (relative risk 10.52 and 2.18, respectively) [63]. This meta-analysis reinforced the importance of adopting WHO recommendation for exclusive breastfeeding during the first 6 months of life as a key child survival intervention, especially in developing countries.

Few studies evaluated the association between breastfeeding and hospitalization risk, with conflicting results. Tarrant, M. et al. found that breastfeeding for at least 3 months was associated with a lower risk of hospital admission in the first 6 months of life for gastrointestinal infections [33], while Davisse-Paturet, C. et al. showed that a shorter duration of breastfeeding (any breastfeeding for less than 3 months) was associated with higher risks of hospitalizations from gastrointestinal infections [57]. Differently, in a Japanese longitudinal study breastfeeding was not associated with reduced risk of hospitalization for diarrhea [32]. Interestingly, a Japanese cohort study (31,578 term and late-preterm infants; follow-up 18 months of life) found that exclusively breastfed late preterm infants did not show an increased risk of hospitalization for gastrointestinal infection, suggesting that exclusive breastfeeding probably mitigates the adverse effect of late preterm birth on gastrointestinal infections [26].

As for respiratory tract infections, breastfeeding duration seems to influence the risk of contracting gastrointestinal diseases. Raheem, R.A. et al. found that infants who are predominantly breastfed for longer duration have lower risks of having diarrhea [39]. In comparison with never breastfeeding, predominant breastfeeding for 4–6 months was associated with lower risk of gastroenteritis in the first 6 months of life (OR 0.34); this finding may at least in part be explained by exposure to higher doses of long-chain polyunsaturated fatty acids received from colostrum and human milk [40]. Finally, if considering specifically Rotavirus infection, a meta-analysis of six studies (3466 children) found that exclusive breastfeeding significantly reduces the risk of Rotavirus infection (OR 0.62) among children below 2 years of age [64].

1.3. Breastfeeding and Immunodeficiency Virus

Breastfeeding promotion for infants born from immunodeficiency virus (HIV)-infected mothers is a still highly debated topic, with important repercussions for public health strategies [65]. WHO in 2010 first recommended antiretroviral therapy (ART) to prevent HIV postnatal transmission through breastfeeding [66]. Subsequently, lifelong ART has been recommended for everyone from the time when any adult (including pregnant and breastfeeding women) or child is first diagnosed with HIV infection [67]. However, national guidelines for high-income countries generally discouraged women living with HIV from breastfeeding their infants. In 2013 the American Academy of Pediatrics recommended that pregnant women need to be aware of the potential risk of HIV transmission to infants from breastfeeding. In the United States, HIV-infected women should be counseled not to breastfeed, regardless of ART use or viral load. Moreover, HIV seronegative women who are at high risk of seroconversion should repeat HIV testing and receive education about the risk of HIV transmission through human milk and should be provided an individualized recommendation concerning the appropriateness of breastfeeding [68]. Similarly, the Centers for Disease Control and Prevention (CDC) recommended that HIV-infected mothers completely avoid breastfeeding their infants, regardless of ART and maternal viral load, providing feeding guidance and emotional support for mothers living with HIV that experienced social or cultural pressure to breastfeed. Indeed, CDC pointed out that keeping an undetectable viral load significantly reduces, but does not completely eliminate, the risk of transmitting HIV through breastfeeding [69].

On the contrary, in 2016 WHO recommended that HIV-infected mothers (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed for the first six months of life. Mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or longer (similar to the general population) while being supported for ART adherence. WHO highlighted that this guideline is intended mainly for low- and middle-income countries with high HIV prevalence and settings in which diarrhea, pneumonia, and undernutrition are common causes of infant and child mortality [70]. Despite this clear division between recommendations for high- and low-income countries, breastfeeding from mothers living with HIV has been recommended also in high-resource settings [71][72]. Moreover, a recent systematic review reiterated that exclusive breastfeeding had a positive outcome on growth and development of all infants irrespective of HIV status [73]. Therefore, in absence of definitive and universally shared recommendations, health care professionals should provide adequate counseling and support to women living with HIV who desire to breastfeed, discussing benefit-risk ratio and supervising adherence to ART [74].

2. Vitamin D Supplementation in Childhood

The term “vitamin D” is commonly used to indicate two different forms which are found in nature: vitamin D_3 (cholecalciferol) from animal sources and vitamin D_2 (ergocalciferol) from plants. Humans can produce vitamin D_3 in their skin in response to sunlight exposure, while vitamin D_2 and D_3 may be obtained from dietary sources. Vitamin D is usually called the sunshine vitamin because most of the vitamin D we synthesize (90%) derives from skin exposure to solar ultraviolet B radiation, while the contribution of dietary intakes, with the exclusion of artificially fortified foods, may be considered negligible [75][76].

Vitamin D supplementation is the simplest and safest way to prevent nutritional rickets and, more generally, vitamin D deficiency at every age of life. Besides this historically well-known indication, considering the growing interest on skeletal and extra-skeletal actions of vitamin D, supplementation has been proposed to promote both bone and general health of children and adults, even if actual evidence from human studies suggest that supplementation of vitamin D-replete individuals does not provide demonstrable health benefits [77].

Vitamin D supplementation is essential to ensure an adequate vitamin D status during the first year of life, because newborns and infants should be poorly exposed to solar light and vitamin D content of breast and formula milk are both insufficient. Even if breast milk is the best food to satisfy children’s nutritional needs, it contains a poor amount of vitamin D (<50 IU/L) [78]. On the other hand, vitamin D intake of non-breastfed infants depends on vitamin D formula content (about 400 IU/L) and daily formula intake. Considering water requirements, formula-fed infants may receive 400 IU/day of vitamin D only when they weigh 5–6 Kg, so only some months after birth and near weaning, when daily milk consumption inevitably reduces [79]. Finally, as fetal vitamin D stores depend exclusively on maternal vitamin D status, newborns from mothers not receiving vitamin D supplementation and with poor sun exposure are at increased risk of vitamin D deficiency [80]. For all these reasons, first an expert position statement [79], followed by international [81] and national consensus [82] recommended vitamin D supplementation with 400 IU/day for all infants from birth to 12 months of life, independently of their mode of feeding. A recent meta-analysis (19 studies with 2837 mother–infant pairs) confirmed that vitamin D supplementation with 400 IU/day was effective to prevent vitamin D deficiency in high-risk term breastfed infants [83]. Another meta-analysis (28 trials with an overall sample size of 5908 participants of maternal–infant dyads) found that maternal postpartum or infant intermittent vitamin D supplementation may represent plausible substitutes for daily infant vitamin D supplementation in breastfed infants, but actual evidence remains too weak to support a policy update [84] and daily infant vitamin D supplementation remained mandatory during first and second infancy.

As nutritional rickets may develop during the entire pediatric age and an inadequate vitamin D status may negatively affect bone health, beyond 1 year of age vitamin D supplementation with at least 600 IU/day is recommended in children and adolescents with risk factors for deficiency [81]. A recent review confirmed that universal vitamin D supplementation until 12 months of age is strongly recommended, while beyond 1 year of life supplementation is recommended only in at-risk children. However, the authors highlighted that this age cut off is essentially arbitrary and not based on robust evidence, therefore the length of supplementation should always be individualized [85]. Risk factors for hypovitaminosis D identified from the Italian Pediatric Society are resumed in **Table 1**, while **Table 2** summarizes the indications for vitamin D supplementation during childhood [82].

Table 1. Risk factors for vitamin D deficiency in childhood [82].

First Year of Life	1–18 Years
Non-Caucasian ethnicity with dark skin pigmentation	
Inadequate diets (i.e., vegan diet)	
Chronic kidney disease	
Hepatic failure and/or cholestasis	
Malabsorption syndromes (i.e., cystic fibrosis, inflammatory bowel diseases, celiac disease at diagnosis)	
Chronic therapies: anticonvulsants, systemic glucocorticoids, antiretroviral therapy, systemic antifungals (i.e., ketoconazole)	
Infants born from mothers with multiple risk factors for vitamin D deficiency, particularly in absence of vitamin D supplementation during pregnancy	Reduced sunlight exposure (due to lifestyle factors, chronic illness or hospitalization, complex disability, institutionalization, covering clothing for religious or cultural reasons) and/or constant use of sunscreens
	International adoption
	Obesity

Table 2. Key points of vitamin D supplementation in childhood [82].

First Year of Life	1–18 Years
Vitamin D supplementation is recommended in all newborns, independently of the type of feeding.	Vitamin D supplementation is recommended in children and adolescents with risk factors for vitamin D deficiency.
Vitamin D supplementation should be started within the first days of life and continued throughout the first year.	Vitamin D supplementation is recommended from the end of fall to the beginning of spring (November–April) in children and adolescents with reduced sun exposure during summer. Continuous vitamin D supplementation is recommended in cases of permanent risk factors for vitamin D deficiency.
Infants born at term without risk factors for vitamin D deficiency should receive 400 IU/day of vitamin D. In the presence of risk factors for vitamin D deficiency up to 1000 IU/day of vitamin D can be given.	At-risk children should receive daily vitamin D supplementation ranging from 600 IU/day (i.e., in presence of reduced sun exposure) up to 1000 IU/day (i.e., in presence of multiple risk factors for vitamin D deficiency).
Daily administration of vitamin D is recommended.	In cases of poor compliance, supplementation with intermittent dosing (weekly or monthly doses for a cumulative monthly dose of 18,000–30,000 IU of vitamin D) can be considered, starting from children aged 5–6 years and particularly during adolescence.

First Year of Life	1–18 Years
Individuals on anticonvulsants, oral corticosteroids, antimycotics and antiretroviral drugs should receive at least 2–3 times more vitamin D than the daily requirement recommended for age.	
Vitamin D metabolites and their analogs (calcifediol, alfacalcidol, calcitriol, and dihydrotachysterol) are not recommended for the routine vitamin D supplementation.	
25(OH)D testing in children and adolescents is not recommended. Evaluation of serum 25(OH)D levels can be considered in presence of multiple risk factors for vitamin D deficiency. Vitamin D status should be monitored at least yearly in subjects that require continuous supplementation.	

Vitamin D and Infections

Vitamin D, due to its complex immunoregulatory properties, modulates innate and adaptive immunity and inflammatory response. A detailed discussion of the immunological effects of vitamin D is beyond the scope of this research and can be found elsewhere [86][87][88]. Briefly, vitamin D stimulates innate immunity by increasing the production of cathelicidin and β-defensins, as well as enhancing chemotaxis and phagocytosis. At the same time, vitamin D reduces the synthesis of pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and Th1 and Th17 cells response, favoring Th2 cells activity with consequent anti-inflammatory effect due to increased production of IL-4, IL-5, IL-10, IL-13 [87].

Several observational studies found a relationship between vitamin D status and incidence or severity of upper- and lower-respiratory tract infections in children, both in developing and in westernized countries [89][90][91]. However, a possible association between severe vitamin D deficiency and respiratory tract infections was historically hypothesized due to the identification of a significant increased risk of pneumonia and respiratory complications in rachitic children, a condition known as rachitic lung [92][93][94]. A significant association between 25-hydroxyvitamin D [25(OH)D] levels and other pediatric infections has also been found, including urinary tract infections [95], otitis media [96], acute diarrhea [97], rotavirus infection [98], malaria [99], leishmaniosis [100], hepatitis C [101], and sepsis [102][103][104]. Moreover, some studies investigated a possible relationship between vitamin D deficiency and tuberculosis infection in children, with discordant results [105][106]. Even if vitamin D supplementation does not seem to have any beneficial effect in the treatment of tuberculosis in children and adults [107], an individual-participant data meta-analysis showed that vitamin D predicts tuberculosis disease risk in a dose-dependent manner and tuberculosis risk was highest among HIV-positive individuals with severe vitamin D deficiency [108].

Despite a growing number of studies assessing the relationship between vitamin D status and infections risk, it is still unclear whether vitamin D deficiency should be considered a consequence of the infection or if it plays a causative role in increasing infections risk. More robust evidence was expected from supplementation studies, but several variables may confound the results and complicate the comparison between different studies (i.e., differences in population enrolled, vitamin D supplementation dosage and regimen, length of follow-up, and percentage of enrolled individuals with severe vitamin D deficiency).

Most of meta-analyses confirmed a significant protective role of vitamin D supplementation against respiratory infections; particularly, major benefits were observed in children and adolescents, asthmatic subjects, individuals with severe vitamin D deficiency, and those receiving a daily dosing regimen (400–1000 IU/day) for a duration of 12 months or less.

A systematic review of observational studies and randomized controlled trials (RCTs) focusing on extra-skeletal actions of vitamin D confirmed that vitamin D supplementation plays a significant role in the primary prevention of acute respiratory infections [109]. Preventive efficacy of vitamin D supplementation was particularly evident in subjects with severe deficiency [25(OH)D < 10 ng/mL], while vitamin D administration was not effective as adjunctive treatment of acute respiratory infections [110][111][109]. An expert consensus statement from the World Association of Infectious Diseases and Immunological Disorders confirmed that vitamin D could play a role in children with recurrent respiratory infections. However, future large and methodologically adequate studies in predisposed children are needed to clearly identify the lowest serum vitamin D level associated with a significant increased risk of respiratory infections, in adjunct with the most effective dosage, regimen and duration of vitamin D supplementation [112]. Similarly, an Italian inter-society consensus on the prevention of recurrent respiratory infections found that reduced vitamin D levels are associated with an increased incidence of viral respiratory infections in the first years of life [113]. Even if the evidence was too low to universally recommend vitamin D supplementation only for the prevention of respiratory infections, populations with low socioeconomic status and severe vitamin D deficiency, and children with recurrent acute otitis may benefit from vitamin D supplementation for such purpose. Finally, a recently published review of meta-analyses and RCTs confirmed that individuals most likely to benefit from supplementation are those with baseline vitamin D deficiency or with selected high-risk conditions [114].

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