



World Health  
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# Nutritional rickets

A REVIEW OF DISEASE BURDEN, CAUSES, DIAGNOSIS,  
PREVENTION AND TREATMENT







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Nutritional rickets: a review of disease burden, causes, diagnosis, prevention and treatment

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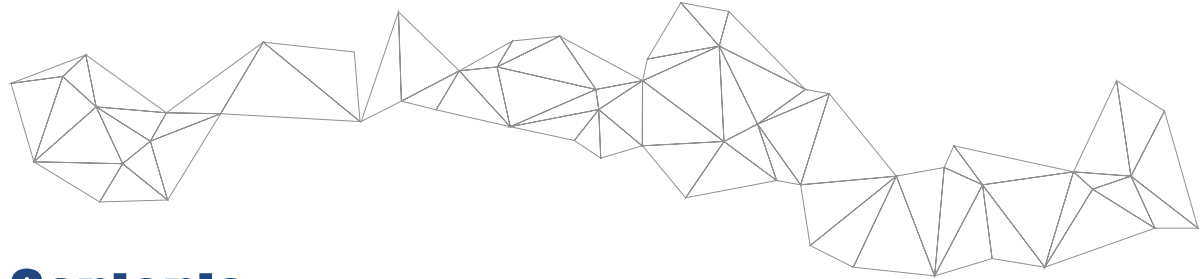
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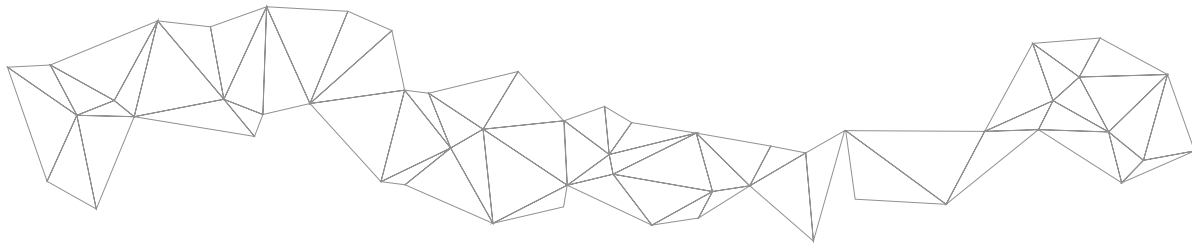
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# Contents

<b>Acknowledgements</b>	<b>IX</b>
<i>Financial support</i>	<b>IX</b>
<b>Abbreviations</b>	<b>X</b>
<b>Introduction</b>	<b>1</b>
<i>Background</i>	<b>2</b>
<i>Scope and purpose</i>	<b>2</b>
<b>What is rickets?</b>	<b>3</b>
<i>History of diagnosis of rickets</i>	<b>4</b>
<i>Development of rickets</i>	<b>4</b>
<b>The magnitude and distribution of nutritional rickets: disease burden in infants, children and adolescents</b>	<b>7</b>
<i>Screening and diagnosis of nutritional rickets</i>	<b>8</b>
<i>The prevalence of rickets in infants, children and adolescents</i>	<b>15</b>
<b>Understanding the diverse causes or determinants of nutritional rickets</b>	<b>19</b>
<i>Vitamin D status</i>	<b>20</b>
<i>Calcium status</i>	<b>29</b>
<i>Other nutritional causes</i>	<b>32</b>
<i>Preterm birth and low birth weight</i>	<b>32</b>
<b>Developing solutions or interventions that could prevent or mitigate nutritional rickets in infants, children and adolescents</b>	<b>33</b>
<i>Screening</i>	<b>34</b>
<i>Prevention of nutritional rickets</i>	<b>35</b>
<i>Treatment of nutritional rickets</i>	<b>37</b>
<b>Implementing or delivering solutions through policies and programmes</b>	<b>39</b>
<i>Regulatory considerations</i>	<b>40</b>
<i>Ethical considerations</i>	<b>41</b>
<b>Evaluating the actions for prevention or treatment of nutritional rickets</b>	<b>43</b>
<b>Knowledge gaps</b>	<b>45</b>
<b>Final considerations</b>	<b>46</b>
<b>References</b>	<b>47</b>





## Acknowledgements

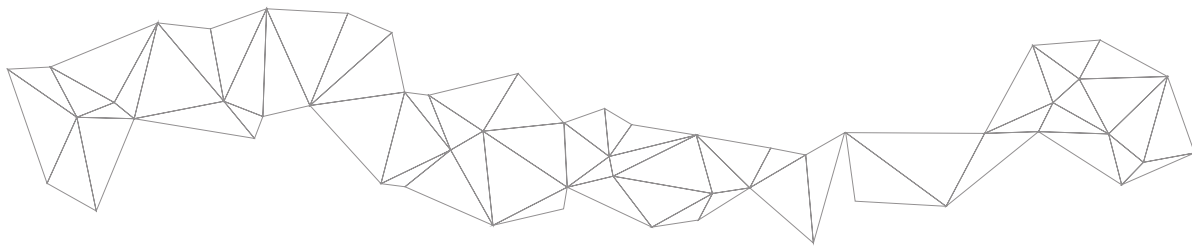
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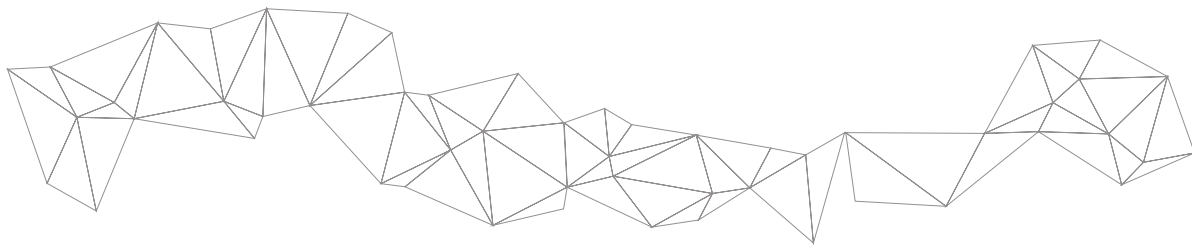
# Abbreviations

<b>25(OH)D</b>	25-hydroxycholecalciferol
<b>1,25(OH)<sub>2</sub>D</b>	1,25-dihydroxycholecalciferol
<b>CDC</b>	United States Centers for Disease Control and Prevention
<b>DACH</b>	the joint committee for nutritional recommendations in Germany, Austria and Switzerland
<b>EFSA</b>	European Food Safety Authority
<b>FAO</b>	Food and Agriculture Organization of the United Nations
<b>GINA</b>	Global database on the Implementation of Nutrition Action
<b>IOM</b>	Institute of Medicine
<b>LC-MS</b>	liquid chromatography–tandem mass spectrometry
<b>NNR</b>	Nordic Nutrition Recommendations
<b>PTH</b>	parathyroid hormone
<b>RDA</b>	recommended daily allowance
<b>RNI</b>	recommended nutrient intake
<b>SACN</b>	Scientific Advisory Committee on Nutrition
<b>UK</b>	United Kingdom of Great Britain and Northern Ireland
<b>USA</b>	United States of America
<b>UV</b>	ultraviolet
<b>VDDR-I</b>	type I (hypocalcaemic) vitamin D-dependent rickets
<b>VDR</b>	vitamin D receptor
<b>VMNIS</b>	Vitamin and Mineral Nutrition Information System
<b>WHO</b>	World Health Organization





# **INTRODUCTION**



## Background

Rickets is a disease that occurs in growing children, owing to failure of mineralization of the growth plate and osteoid matrix (1–4). Specifically, it results in defective chondrocyte differentiation and mineralization of the epiphyseal growth plates and defective osteoid mineralization. Bone matrix formation as well as mineralization is also delayed, leading to an accumulation of unmineralized matrix on microscopic bone surfaces (5). The skeleton then loses its stiffness and becomes severely deformed (bowed legs and misshapen pelvis), ultimately leading to stunted growth. Clinical and radiological features of widened growth plates are usually used to diagnose rickets. The main causes of rickets are deficient intakes of vitamin D and/or calcium, or physiological problems associated with the metabolism of these nutrients. The peak incidence of rickets occurs among infants and young children aged 6–23 months and adolescents aged 12–15 years, though it may also occur in children aged between 2 years and 11 years (6–9).

Rickets in childhood has devastating consequences but these are often poorly recognized by health systems and in society. It is associated mainly with growth problems, bone pain, muscle weakness, limb and pelvic deformities, failure to thrive, developmental delay (such as gross motor delays in sitting, crawling and walking) and dental anomalies (8–12). In addition, rickets results in poor sleep and restlessness (13) and could delay eruption of the deciduous teeth, which then alters the sequence of eruption, affecting mainly the permanent incisors, cuspids and first molars (14). In the long term, rickets could lead to osteomalacia (abnormal matrix mineralization in established bone), low bone mass in adulthood and narrowing of the pelvic outlet, which then can result in obstructed labour and maternal and fetal death (4).

## Scope and purpose

This document aims to provide a literature review of nutritional rickets among infants, children and adolescents. It is intended to provide stakeholders with a summary of the aspects surrounding rickets in public health, including the burden of rickets and its causes, diagnosis, prevention and treatment.

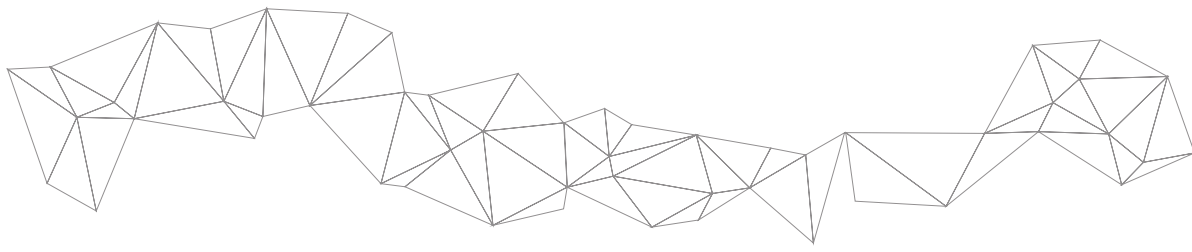
This document is not a World Health Organization (WHO) guideline. It is a literature review that also includes the history of rickets epidemiology, the pathophysiology of the condition, and issues related to its diagnosis and consequences.

As most cases of nutritional rickets are caused by low vitamin D intake and sun exposure and/or low calcium intake, the document focuses on nutritional rickets and discusses the physiology, functions and epidemiology of vitamin D and calcium deficiency and food sources of these nutrients. The current WHO recommendations for calcium and vitamin D in different populations and settings are discussed. This publication supports the [Comprehensive implementation plan on maternal, infant and young child nutrition](#) (15), calling for an update of the evidence for nutrition actions, in line with [The global strategy for women's, children's and adolescents' health \(2016–2030\)](#) (16). The document provides a review of nutritional rickets in infants, children and adolescents, using the approach suggested by [The WHO strategy on research for health](#) (17). Applying this strategy, the document covers the following areas:

1. overview of the history and epidemiology of rickets;
2. the magnitude and distribution of nutritional rickets in the population, especially in infants, children and adolescents;
3. the causes or determinants of rickets, whether they are biological, behavioural, social or environmental factors;
4. potential interventions to prevent or mitigate nutritional rickets in infants, children and adolescents;
5. implementation or delivery of solutions through nutritional policies and programmes;
6. evaluation of the actions for prevention or treatment of nutritional rickets; and
7. current research gaps.



## **What is rickets?**



## History of diagnosis of rickets

The first recorded references to rickets date back to the first and second centuries, when the Greek physicians Soranus of Ephesus and Claudius Galenus reported observations of a bone deformity similar to those associated with rickets in Roman children (18). Thereafter, there were isolated reports until this condition was properly identified in the 17th century in England by Francis Glisson and published in 1651 as the *Tractatus de rachitide* (Treatise of rickets) (18).

Case-reports on rickets started to increase from the late 18th century and beginning of the 19th century in England and later in other European countries and in the United States of America (USA), almost in parallel with the Industrial Revolution (18). It became endemic by the 20th century, particularly in the industrialized cities of northern Europe (19). In the 1800s, physicians and scientists made the observations that rickets was more common in children living in cities, compared to those living in rural areas; in regions with extreme latitudes and with variations in the seasons; as well as among those with food deficiencies. This led to a conclusion that inadequate sun exposure was one of the main causes of rickets (19). In this period, lack of a “white salt” (later identified as calcium) and a lipid-based substance in the diet was also identified as being associated with rickets (18). French and German physicians also noted that rickets could be cured with cod liver oil (or any other fish oil) or by sun exposure (18, 20, 21).

In 1904, the Scottish pediatrician Robert Hutchison published the *Lectures on the diseases of childhood*, in which he attributed rickets to three main factors: difficulties of breastfeeding; increase in the number of working mothers in factories, leaving children at home all day without adequate food; and living in populous contaminated cities (22). He recommended increasing the intake of milk proteins and fats, egg yolks and raw meat juice, and increasing exposure to sunlight.

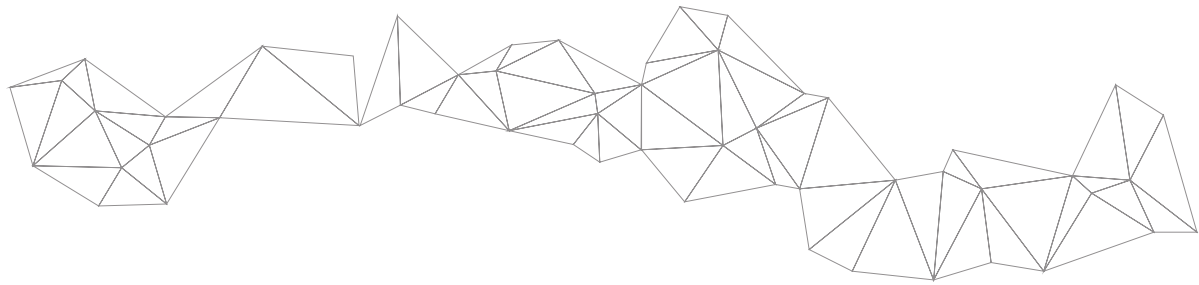
In the 1920s, vitamin D was identified by McCollum and colleagues as the anti-rachitic substance (23–25), which was a very important step towards understanding this condition and how to prevent and treat it (18, 26, 27). At this point, it was known that vitamin D is necessary for absorption and utilization of calcium, explaining the effect of this vitamin as the anti-rachitic substance. It took further time to discover that there were two forms of the vitamin. In the 1930s, it became clear that ergocalciferol (vitamin D<sub>2</sub>) came from foods, while colecalciferol (vitamin D<sub>3</sub>) was synthesized in skin by irradiation from sunlight, from a precursor (7-dehydrocholesterol) (18). Later, it was established that colecalciferol was not a vitamin but rather a steroid hormone, although it continues to be designated as a vitamin to this day.

The addition of vitamin D (i.e. vitamin D<sub>2</sub> or vitamin D<sub>3</sub>) through fortification of some staple foods started in the 20th century in a few countries, and rickets was virtually eradicated from those countries that implemented this intervention (19–21).

## Development of rickets

In healthy infants and children, the growth plates are differentiated in an orderly fashion, with several steps and factors involved in this process. First, cartilage cells in the resting zone of the growth plate mature into chondrocytes, and this occurs progressively from the epiphysis to the metaphysis. Then, these chondrocytes are organized into columns, aligned along the longitudinal axis, and undergo hypertrophy (28). The differentiated hypertrophic chondrocytes are then vascularized, undergo apoptosis, are mineralized, and eventually are turned into primary spongiosa – the spongy substance of bone that contains mineralized tissue, marrow and cartilage – by the osteoclasts (28).

In rickets, there is impaired vascularization, chondrocyte apoptosis, and mineralization of the cartilage matrix surrounding the apoptotic chondrocytes. The accumulation of hypertrophic chondrocytes in the growth plate, which occurs as a result of delayed chondrocyte apoptosis, leads to a loss in their columnar arrangement and, therefore, disorganization of the growth plate (29). The end result is hypertrophy of the



costochondral junctions, swelling at the end of long bones, and widening of metaphyses, cortical thinning, and impaired remodelling (28).

Because bone mineralization requires an adequate supply of calcium and phosphate, nutritional rickets can be related to low intake of calcium, vitamin D or phosphorus. Nutritional rickets due to low calcium and/or vitamin D intake is the most common (3, 4, 28, 30, 31). Vitamin D deficiency can be caused by inadequate intake due to dietary factors (e.g. special diets [veganism], lactose intolerance or allergies) and/or limited exposure to sunlight due to geographic location, sun avoidance or shiftwork. Severe deficiency results in disordered bone modelling, called rickets in childhood (open growth plates) and osteomalacia in adults (fused growth plates) (32). Rickets can also be caused by an abnormality in phosphorus homeostasis, owing to genetic mutations, leading to low serum phosphate levels (28). Low serum phosphate levels lead to rickets, as phosphate is one of the major components of the skeleton, providing mineral strength to bone. Hypophosphataemic rickets is a group of genetic diseases characterized by hypophosphataemia, rickets and normal serum levels of calcium (33). Rickets associated with chronic hypophosphataemia is mostly genetic and usually presents after 1–2 years of age.

In children with rickets due to vitamin D deficiency, calcium absorption is impaired, as vitamin D is needed for active calcium absorption by upregulation of the synthesis of proteins needed to transport calcium across the intestinal cells. This stimulates the secretion of parathyroid hormone (PTH), which increases calcium reabsorption in the kidneys; stimulates  $1\alpha$ -hydroxylase enzyme activity to increase the synthesis of 1,25-dihydroxycholecalciferol ( $1,25(\text{OH})_2\text{D}$ ; vitamin  $\text{D}_3$ ); and stimulates urinary phosphorus excretion and calcium mobilization from bone (34). These events result in phosphate deficiency, which first occurs locally around osteoblasts and chondrocytes, leading to the accumulation of hypertrophic chondrocytes in the growth plate, and resulting in the cascade of events as detailed above. The generalized hypophosphataemia also affects other tissues, producing muscle weakness, tenderness and pain (5). If this state persists, hypocalcaemia may become evident again, ultimately resulting in bone deformity and bone pain, owing to hydration and swelling of the demineralized collagen matrix, which causes the periosteal covering to expand outward. Hypocalcaemic (type I) vitamin D-dependent rickets (VDDR-I) is an early-onset hereditary disorder of vitamin D metabolism, characterized by severe hypocalcaemia leading to osteomalacia and rachitic bone deformations, and moderate hypophosphatemia (35). Hypocalcaemic vitamin D-resistant rickets is a hereditary disorder of vitamin D action characterized by hypocalcaemia, severe rickets and, in many cases, alopecia (36).

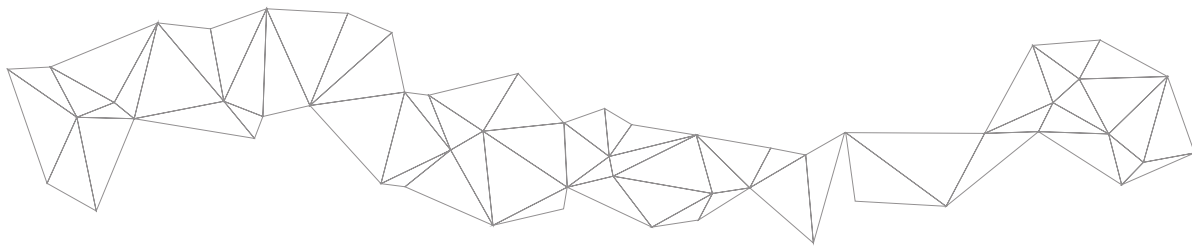
The final stages of hypocalcaemia could lead to seizures or tetany. This occurs more frequently during periods of greater growth velocity (infancy and adolescence), as the demands for calcium cannot be met during these periods. In contrast, in periods of slower growth velocity, hypocalcaemia may not be evident, as it could be corrected in time by the cascade of events triggered by PTH; however, low availability of calcium at that stage of development results in bone demineralization and undermineralization of bone matrix and may lead to lower bone mass and bone deformities. Vitamin D deficiency in combination with hypocalcaemia may manifest clinically as wheezing, hypotonia, muscular weakness, brisk reflexes and cardiomyopathy. Low calcium intake can also increase levels of  $1,25(\text{OH})_2\text{D}$ , which may directly impair matrix mineralization and delay chondrocyte maturation (30).

Rickets associated with vitamin D deficiency usually occurs between 6 months and 2 years of age, while rickets associated with very low calcium status usually occurs in older children, when breastfeeding stops. In adolescents, rickets may be related to low calcium status, vitamin D deficiency, both, or phosphorus deficiency.





# **THE MAGNITUDE AND DISTRIBUTION OF NUTRITIONAL RICKETS: DISEASE BURDEN IN INFANTS, CHILDREN AND ADOLESCENTS**



**C**lear screening and diagnostic definitions for nutritional rickets are needed to be able to quantify the magnitude of the problem worldwide, to compare prevalence figures between populations, to develop appropriate guidelines for its prevention and treatment and to evaluate interventions. The criteria for screening and diagnosis of nutritional rickets should be simple, reproducible and affordable across different regions of the world, with a reasonable degree of sensitivity (30).

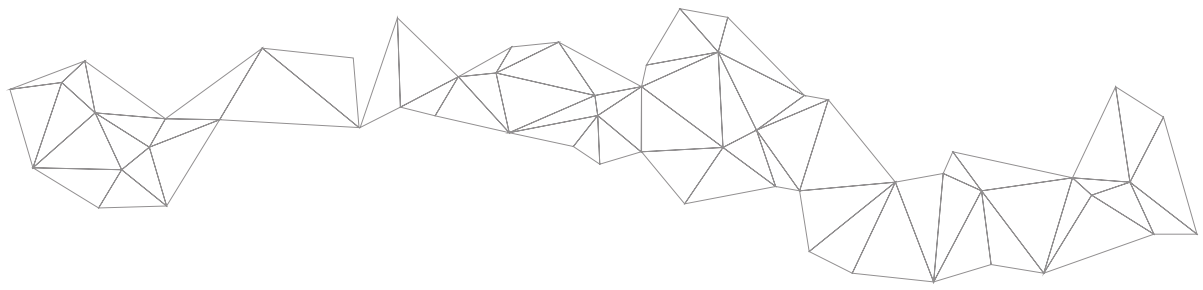
### **Screening and diagnosis of nutritional rickets**

Currently, there are no internationally accepted diagnostic criteria for rickets, although a consensus group, representing 11 international scientific organizations, not including WHO, participated in a multiday conference in May 2014 to reach a global evidence-based consensus on the diagnostic criteria for rickets and osteomalacia (4). In general, rickets has been screened and diagnosed based on a combination of parameters, including health history (e.g. breastfeeding, calcium intake, use of vitamin D and calcium supplements) and clinical signs based on physical examination, biochemical testing and radiographs. Radiographs have been traditionally considered to be the gold standard in diagnosing rickets. The presence of these parameters often changes depending on the stage of disease. In 1976 (31), rickets was divided into three general stages (with variations depending on age and other factors):

- *early or initial stage*, in which there is osteopenia; hypocalcaemia (usually transient) or normal serum calcium concentrations; hypophosphataemia or normal blood phosphorus concentrations; an increase in serum alkaline phosphatase (compared to age-specific reference ranges), which is very sensitive to rickets; an increase in PTH concentrations; and a decrease in plasma 25-hydroxyvitamin D (25-hydroxycholecalciferol; 25(OH)D) concentrations;
- *moderate or second stage*, in which there are initial radiographic signs of rickets (such as bowing deformities of the legs and widening of the wrists) with concomitant hydration and swelling of the collagen matrix, expansion of the periosteal covering and bone pain; hypocalcaemia or normal serum calcium concentrations due to bone calcium mobilization stimulated by the increase in PTH; clear hypophosphataemia; a moderate increase in alkaline phosphatase and PTH; and a greater decrease in plasma 25(OH)D concentrations;
- *severe or final stage*, in which bone changes become more severe; hypocalcaemia is evident; hypophosphataemia is more severe, as well as the increase in alkaline phosphatase and PTH; and there is a more severe decrease in plasma 25(OH)D concentrations.

It is not easy to identify all cases of rickets, as the early stages of the condition may be undetected by some screening tools, while the later stages may be more readily detected (30). If only clinical examinations are performed, children with active rickets (apparent by biochemical abnormalities) but without clinical abnormalities could go undetected. Also, cases of rickets in small infants with severe vitamin D deficiency, hypocalcaemic convulsions and low bone mass could go undetected if no abnormalities are as yet evident from clinical or radiographic examinations.



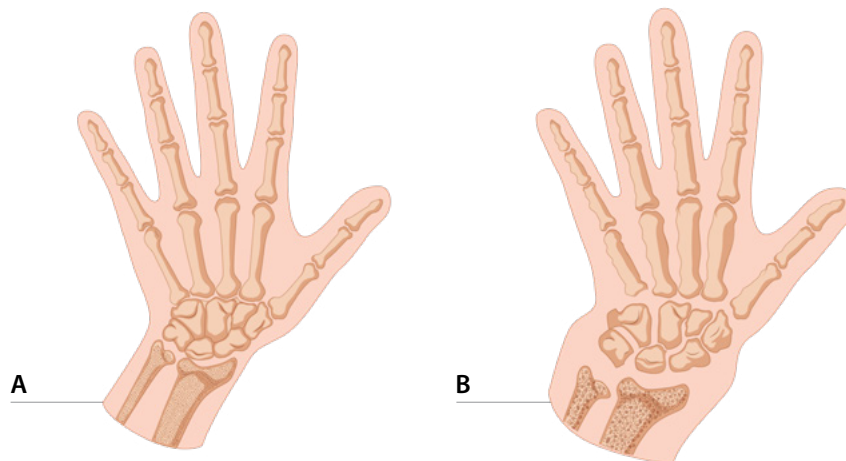


### Clinical signs based on physical examination

Several bone-related features of rickets can be observed clinically, but this varies depending on the age of the child. In infants, the first sign of rickets is a softening or thinning of the skull bones (craniotabes), which is detected by an inward collapse when applying pressure to the skull, typically followed by a snapping back after removing pressure (30). In addition, there is frontal bossing and delayed fontanelle closure (13, 30). In older children, the most common signs are swelling of the wrist (see Fig. 1), knee or ankle, and, as a result of weight-bearing, there could be deformation of the legs such as bowing of the arms, knock-knees (genu valgum), or outward bowing (genu varum) and inability to walk (13). Other signs of rickets include swelling of the costochondral joints of the ribs (rachitic rosary, see Fig. 2), deformity of the soft rib cage, and bone pain. Non-osseous features include convulsions and/or dilated cardiomyopathy, muscular hypotonia, failure to thrive and poor linear growth, delayed motor development, lethargy, irritability, delayed tooth eruption and poor quality tooth enamel, and predisposition to respiratory infections during infancy (3, 4, 7, 29, 31).

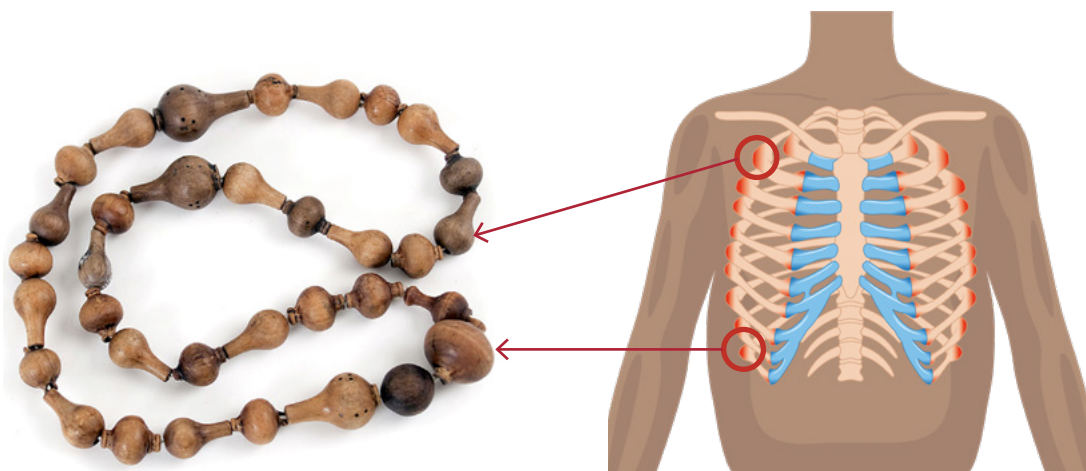
**Fig. 1. Swelling of the wrist in a child with vitamin D-deficiency rickets**

A: normal wrist; B: vitamin D-deficiency rickets

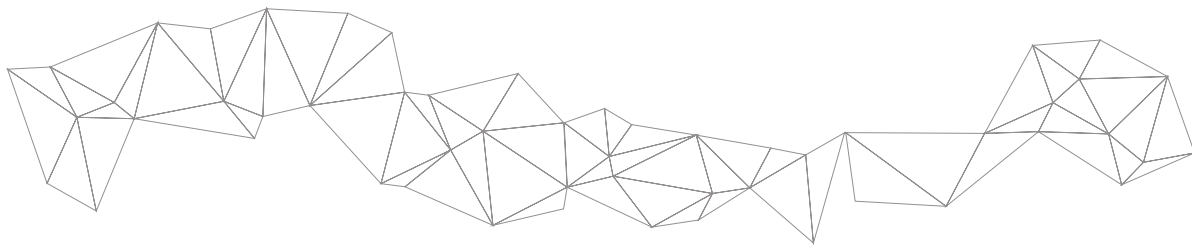


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**Fig. 2. Rachitic rosary: these knobs create the appearance of large beads under the skin of the rib cage, hence the name by analogy with the beads of a rosary**



Source: Medi Photos. Appearance of rachitic rosary by photos (<http://mediphotos.blogspot.com/2011/11/appearance-of-rachitic-rosary-by-photos.html>).



The use of clinical features alone cannot differentiate between children with active rickets and those who are recovering from rickets, or between those with rickets or with other conditions with similar signs (30). In addition, when abnormal bone features are detected clinically, this means the disease is well established. Using only clinical signs could overestimate the prevalence of active rickets, as shown in a study among 6221 children (6 months to 18 years) in Gambia, in which rickets-related bone deformities were found in 196 (3.2%) children but only 3 (1.5%) of them had active rickets based on radiographs (37). Therefore, using clinical signs could lead to unnecessary treatment of rickets in these children, although other treatments should be pursued to treat the deformity.

The sensitivity and specificity of specific clinical signs of rickets have been evaluated against the use of radiographs (as the benchmark diagnosis), with poor results. Among 736 children older than 18 months in Nigeria, only 38% of children with bone deformities or inability to walk had rickets diagnosed radiographically (38). Compared to radiographic features, the positive and negative predictive values for wrist enlargement were 71% and 84%, respectively. For rachitic rosary, the positive and negative predictive values were reported as 56% and 82%, respectively (38). When three or more clinical signs were taken into consideration, the positive predictive value was 73% and the negative predictive value was 89%. It is important to note that positive and negative predictive values are dependent on prevalence; therefore, this way of reporting diagnostic procedures may not be very accurate. Another study in rural China among young children aged 12–24 months found that 41.6% were diagnosed with rickets when using clinical criteria, but based on evaluations of wrist radiographs, more than 70% were diagnosed (39).

The study did not specify the diagnostic criteria used in the evaluation of radiographs. When combining clinical signs, radiographs and biochemical data (25(OH)D levels <30 nmol/L), only 21% were considered to have rickets, which is about half the proportion diagnosed with rickets when only clinical criteria were used.

Since clinical signs lack sensitivity and specificity, they are not reliable for screening or diagnosis.

### Biochemical testing

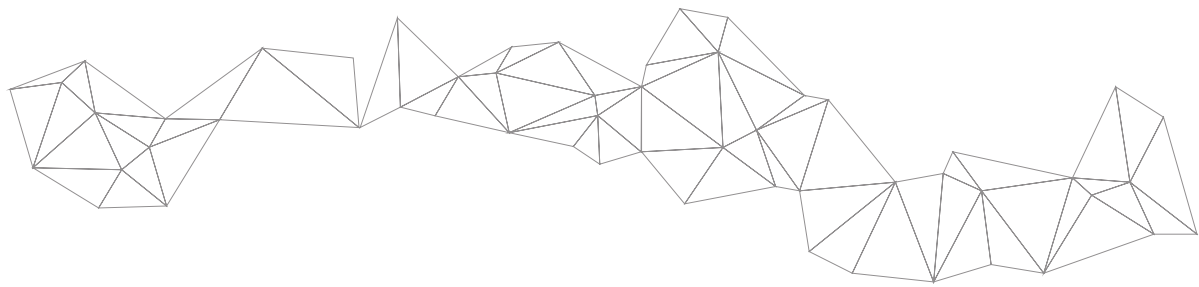
There are several biochemical markers of calcium and vitamin D metabolism that have been considered as screening and/or diagnostic tools for nutritional rickets. These include serum 25(OH)D, serum and urinary calcium levels, serum and urinary phosphate levels, and serum levels of PTH and alkaline phosphatase (3, 4).

#### *Serum 25(OH)D levels*

There is no international consensus on the threshold for serum 25(OH)D for classifying vitamin D status for general health (furthered discussed in [Assessing vitamin D status](#)). However, for rickets, studies have generally found that serum 25(OH)D levels below 30 nmol/L (12 ng/mL) are associated with rickets (40–45), although this may vary depending on the main etiology. In a study in China, serum 25(OH)D levels above 30 nmol/L (12 ng/mL) appeared to prevent rickets in infants with or without vitamin D deficiency at birth (45). However, a recent review of 13 studies of poor to fair quality (one randomized controlled trial, four before-and-after studies and eight case-control studies) found that serum 25(OH) levels associated with rickets ranged from below 30 nmol/L (12 ng/mL) up to 50 nmol/L (20 ng/mL) (46).

Specifically, six of these studies reported that the mean or median serum 25(OH)D level associated with rickets was below 27.5 nmol/L (11.2 ng/mL), while five studies reported that children with rickets had a mean 25(OH)D level above 27.5 nmol/L (11.2 ng/mL) and the other two studies reported at least some children with serum levels above this value. Although different assays were used to measure 25(OH)D levels, inconsistency in the threshold suggests that in these cases, the primary cause of rickets was probably deficient calcium intake and/or a combination of poor vitamin D status and suboptimal calcium intakes.

Unfortunately, dietary calcium intake, as a proxy of calcium status, was either not assessed or the methods for its assessment were not reported; therefore, the levels of serum 25(OH)D associated with rickets could be confounded by dietary calcium intake. In rickets associated with very low calcium intake, serum 25(OH)D levels



may be above 30 nmol/L or within the normal range (47, 48). It is important to note that most children with vitamin D deficiency may not have clinical signs or radiographic features of rickets (49) and this deficiency may be present months before the clinical signs of rickets develop (7).

#### ***Hypocalcaemia (low blood calcium levels)***

The presence of hypocalcaemia in cases of nutritional rickets depends on the stage of the disease. It may be present in the initial stages of rickets, before any physical findings or radiological evidence of rickets. However, blood calcium concentrations may rise during the final stage of rickets. Children with hypocalcaemia may develop laryngospasm, defined as a sudden spasm of the vocal cords, making it difficult to breathe (13). If the hypocalcaemia is severe, it could lead to hypocalcaemic seizures, tetanic spasms, life-threatening hypocalcaemic cardiomyopathy and even heart failure (4).

Hypocalcaemia (including seizures) is a more common manifestation of severe vitamin D deficiency during periods of rapid growth, before 3 years of age or after 10 years of age (29, 50). During these periods, there are increased metabolic demands that are not completely corrected for by the actions of PTH. Growth is slower with a lower metabolic demand, allowing the hypocalcaemia to be transient as the bone is depleted of calcium by the state of hyperparathyroidism (29). This may occur before bone is demineralized during peaks in growth.

#### ***Elevated parathyroid hormone levels***

Elevated concentrations of PTH in serum or plasma are often detected in children with nutritional rickets (51, 52). In children with rickets associated with very low calcium intake, PTH levels have been reported to be less elevated compared to those in children with vitamin D-deficiency rickets (53). The severity of elevated PTH concentrations also depends on the stage of the disease. A systematic review found elevated serum PTH concentrations in children with rickets in six studies, while one study found a negative association between PTH and serum 25(OH)D (46). It is not easy to measure blood PTH concentrations in the community setting, as it is very labile and there can be degradation over time, even if stored at below  $-80^{\circ}\text{C}$  until measured.

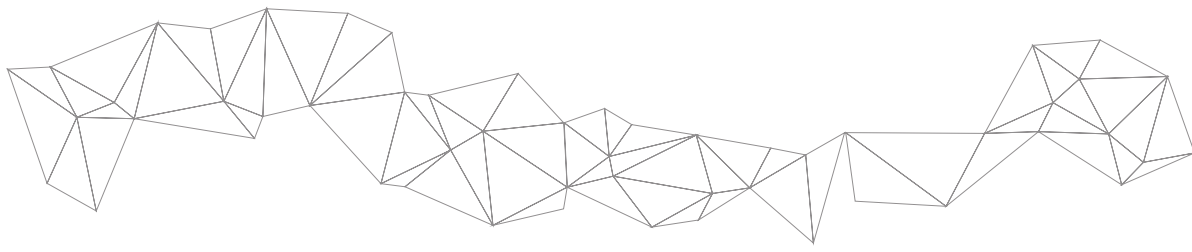
#### ***Hypophosphatemia (low blood phosphate levels)***

Hypophosphataemia is commonly seen in nutritional rickets (29, 30, 54). It has been suggested that low blood phosphate levels are responsible for the growth plate defects in nutritional rickets (55). However, studies have found normal values of serum phosphate in some children with nutritional rickets (52, 56), which also depends on the stage of the disease.

#### ***Elevated blood alkaline phosphatase levels***

An elevated alkaline phosphatase level in serum or plasma is one of the biomarkers most commonly associated with nutritional rickets. Although it is not specific to bone (it is produced by other tissues), in children, the majority of alkaline phosphatase comes from bone. Reference values depend on age and pubertal stage. A study assessing the specificity and sensitivity of elevated serum alkaline phosphatase levels compared to radiographs as a test for rickets among breastfed infants and young children aged 6–15 months, found that concentrations above 552 U/L had a positive predictive value of 40% and a specificity of 97% (57). However, some authors have argued that among those with alkaline phosphatase concentrations above 1000 IU/L, rickets could not be excluded in three of four children in the absence of radiographic changes, as rickets is a dynamic metabolic process and no single screening test may be sufficient to exclude the diagnosis (58). In addition, there were no radiographic abnormalities in children with normal alkaline phosphatase levels, precluding its ability to assess sensitivity.

Another study evaluated the use of this biomarker as a screening tool in 100 Asian children in the United Kingdom of Great Britain and Northern Ireland (UK) – 56 studied retrospectively and 44 studied prospectively (59). Serum alkaline phosphatase, inorganic phosphorus and age predicted the rachitic category with a high



degree of accuracy, with serum alkaline phosphatase being the most important in the discriminant analysis. Other studies in children with rickets have found high blood alkaline phosphatase levels among all children with rickets and significant associations with the severity of the condition (51, 59).

Alternatively, bone-specific alkaline phosphatase measured in serum is sometimes used, although this assay is more expensive and the results may be difficult to interpret, owing to the lack of normative reference ranges in children (30). Studies are needed to evaluate the specificity and sensitivity of these biochemical markers and recommend age-specific reference ranges for total and bone-specific alkaline phosphatase.

### **Radiographs**

Imaging methods, mainly radiographs, have traditionally been used to confirm the diagnosis of rickets and are often considered the gold standard for this purpose. Other imaging diagnostic tools such as magnetic resonance imaging are also used in some settings (60, 61). Abnormal radiographic findings are first evident long after biochemical and histological abnormalities are present.

Radiographs are, therefore, not a suitable tool for screening and prevention of the condition.

During the early stages of the disease, radiographs may show osteopenia and cortical thinning of long bones, followed by widening of the growth plate and an irregular metaphyseal outline like cupping, widening or fraying (4, 29, 34). In infants and young children, the wrists are most affected and rachitic changes as best observed here, while in older children, rachitic changes are more noticeable in the area above and below the knees (63–65). The magnitude of the changes depends on the stage of the condition, with more pronounced changes in the later stages.

To evaluate the degree of metaphyseal fraying and cupping and the proportion of the growth plate affected, some authors developed a 10-point score for wrist and knee radiographs (see Table 1 and Fig. 3) (66). The score increases in half points, ranging from 0 points (normal) to 10 points (severe rickets). This scoring system was evaluated in an intervention study with vitamin D and calcium supplementation among 176 children with nutritional rickets (diagnosed on the basis of clinical, biochemical and radiological features), and showed that it was effective in monitoring the healing of rickets in response to the treatment (67). A study comparing radiological abnormalities with histological abnormalities from autopsies in children found that 38% had histological abnormalities at the growth plate, while only about 6% had radiological abnormalities associated with rickets (68). Therefore, histological changes may be more sensitive than radiographs for diagnosis of rachitic changes at the growth plate (30), but this is not practical, entails ethical concerns, and is not currently done.

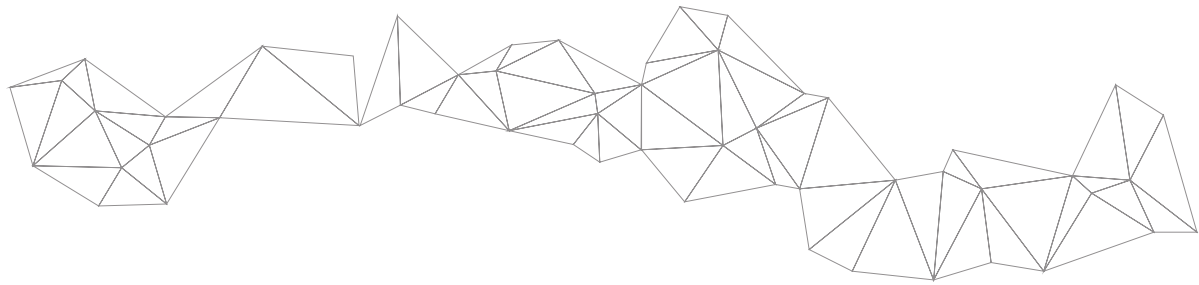
The Japanese Society for Bone and Mineral Research and the Japan Endocrine Society suggest the following indicators to diagnose nutritional rickets (54):

#### **Definite rickets**

- Rachitic changes on radiographs (cupping and fraying of metaphysis, widening of epiphyseal plate)
- High blood alkaline phosphatase
- Hypophosphataemia or hypocalcaemia
- Clinical signs: bone deformities such as genu varum and valgum, abnormal spinal curvature, craniotables, open fontanelles, rachitic rosary, joint swelling

#### **Possible rickets**

- Rachitic changes on radiographs (cupping and fraying of metaphysis, widening of epiphyseal plate)
- High blood alkaline phosphatase
- Hypophosphataemia hypocalcaemia or clinical signs



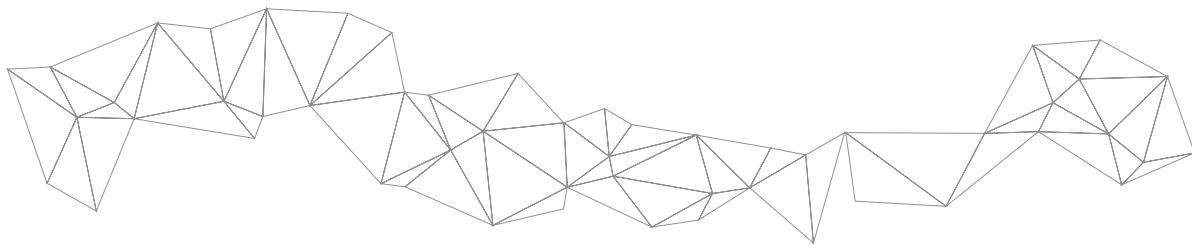
More studies are needed to evaluate the specificity and sensitivity of the radiological scoring system (66) and the indicators proposed by the two Japanese societies.

**Table 1. Ten-point score for wrist and knee radiographs**

<b>WRIST<sup>a</sup> – score both radius and ulna separately</b>		
<b>Grade</b>	<b>Radiographic features</b>	
1	Widened growth plate, irregularity of metaphyseal margin, but without concave cupping	
2	Metaphyseal concavity with fraying of margins	
2 bones × 2 points = 4 points possible		
<b>KNEE<sup>a</sup> – score both femur and tibia separately</b>		
<b>Multiply the grade in A by the multiplier in B for each bone, then add femur and tibia scores together</b>		
<b>A</b>	<b>Grade</b>	<b>Degree of lucency and widening of zone of provisional calcification</b>
	1	Partial lucency, smooth margin of metaphysis visible
	2	Partial lucency, smooth margin of metaphysis not visible
	3	Complete lucency, epiphysis appears widely separated from distal metaphysis
<b>B</b>	<b>Multiplier</b>	<b>Portion of growth plate affected</b>
	0.5	≤2 condyles or plateaus
	1	2 condyles or plateaus
2 bones × 1 point × 3 points = 6 points possible		
Total: 10 points possible		

<sup>a</sup>Score the worst knee and the worst wrist.

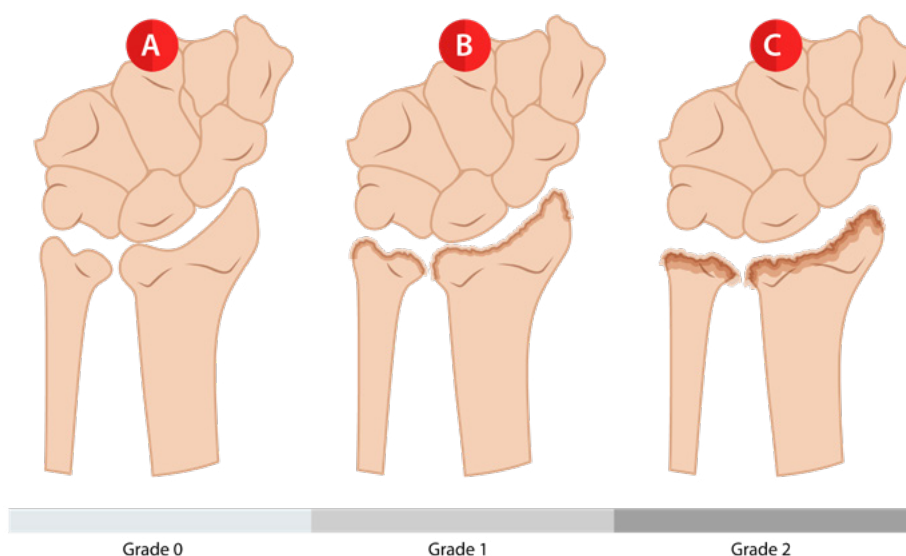
Source: reproduced by permission of the publisher from Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Manaster BJ, Reading JC. Radiographic scoring method for the assessment of the severity of nutritional rickets. *J Trop Pediatr.* 2000;46:132–9 (66).



**Fig. 3. Diagram of varying grades of radiographic changes in rickets**

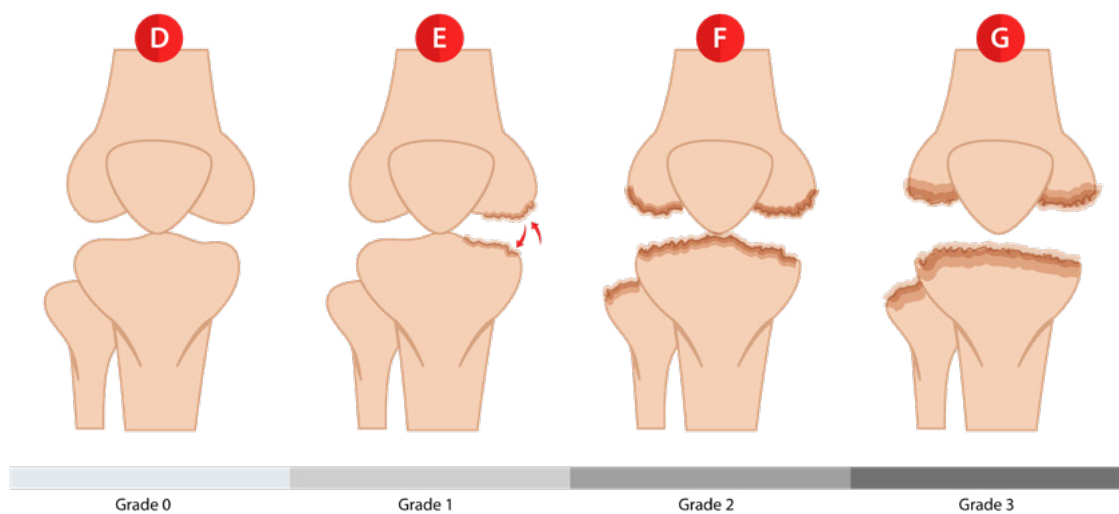
A: a normal wrist; B: irregularity and widening of the growth plate, but without concave cupping; C: concave metaphyseal cupping and frayed margins; D: a normal knee; E: only the medial portions of the femoral and tibial metaphyses are affected; there is partial lucency of the metaphyses, but the margins are clearly visible (arrows); F: partial lucency of the metaphyses, but the margins are not sharply defined; however, the zones of provisional calcification are not completely lucent and display some calcification; G: complete lucency of the zone of provisional calcification; the epiphyses appear widely separated from the distal metaphyses

## WRIST



14

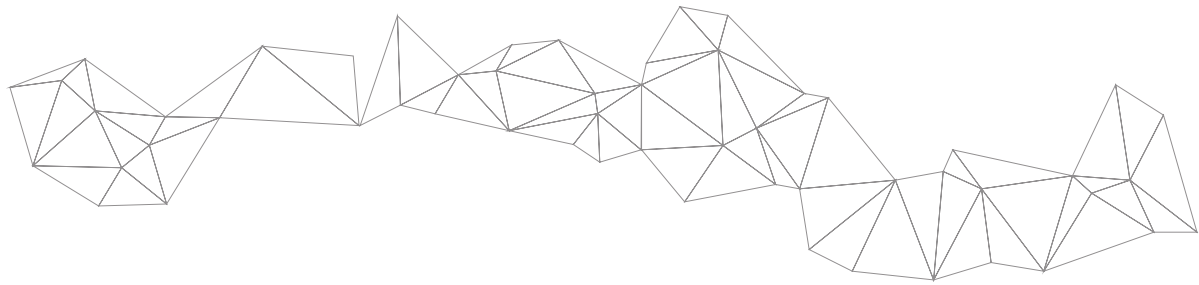
## KNEE



Source: adapted by permission of the publisher from Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Manaster BJ, Reading JC. Radiographic scoring method for the assessment of the severity of nutritional rickets. *J Trop Pediatr.* 2000;46:132–9 (66).

**Nutritional rickets:** a review of disease burden, causes, diagnosis, prevention and treatment





## **The prevalence of rickets in infants, children and adolescents**

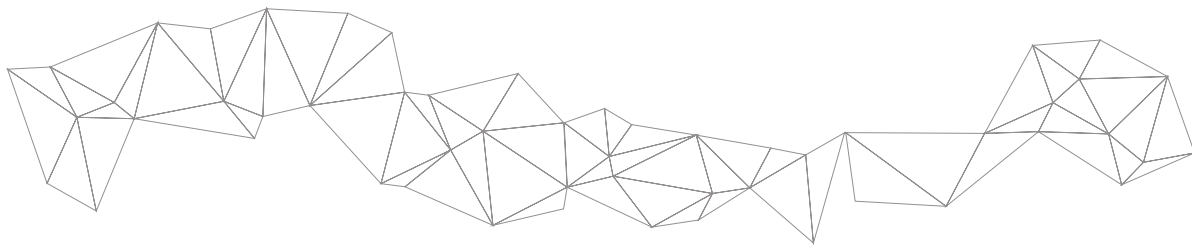
There are currently few population-representative data available on the prevalence of rickets and no national registrations of rickets cases. Prevalence reports usually come from small studies with local or regional reach and the majority of reports are from high-income countries.

In the 1920s and 1930s, it was estimated that the prevalence of rickets was around 75–98% in Europe and the USA (69). Nutritional rickets practically disappeared from industrialized countries when vitamin D food-fortification programmes started (19–21). However, some reports have shown a re-emergence in different countries in the past 10–20 years, probably related to a combination of factors, such as less sun exposure because of the use of sunscreen lotions, skin coverage to avoid skin cancer, and less time spent outdoors in general (70). Also, increased migration of populations across the world, and rural-to-urban migration, is thought to increase the risk of vitamin deficiency, particularly amongst those with a darker skin living in temperate climates (see [Factors that affect vitamin D status](#) for more details). For example, a population-based study conducted in one county in the USA (Olmsted, Minnesota) found a significant increase in the prevalence of rickets from 0 per 100 000 in 1970 to 24.1 per 100 000 in the year 2000 ( $P < 0.01$  for incidence trend) (71). In addition, an analysis of hospitalization reports in England from 1968 found low hospitalization rates for rickets in the 1960s and 1970s, which declined further in the 1980s and 1990s, but increased in the 2000s to the highest rates recorded (72). On the other hand, a decrease in the prevalence of rickets was observed in ethnic Danish children aged 0–2 years (5.0 per 100 000 per year in 1985–1994 down to 2.0 per 100 000 per year in 1995–2005) (69). The authors attribute this reduction to the change in the recommendation by the Danish National Board of Health in 1995 to supplement infants with vitamin D (10 µg/day) from 2 weeks of life until 2 years of age, instead of until 1 year of age in immigrant children.

Table 2 shows data on reported cases of rickets in different countries and populations of infants, children and adolescents. The presence of rickets varies widely between studies. These differences are partly explained by differences in the methods used to diagnose rickets (clinically, biochemically, radiographically or a combination of methods). It is also possible that small studies are targeting areas with a higher prevalence of rickets, overestimating the national prevalence. The lack of consensus on clear diagnostic criteria for rickets complicates the task of quantifying the magnitude of the problem in different communities worldwide (30). Studies not using radiological reports to confirm rickets may be overestimating the prevalence of this condition (30).

For example, a study using a population-based sample in Shanxi Province in China found a prevalence of rickets of 41.6% when diagnosed clinically but 3.7% when diagnosed radiographically (39). However, a population-based study in Gambia found a similar prevalence when using radiographs in combination with biochemical data (3.7%) or using clinical signs of rickets (3.3%) (37). These discrepancies could also be related to the lack of uniformity when assessing radiographs, with possible differences in the interpretation between radiologists and pediatricians.

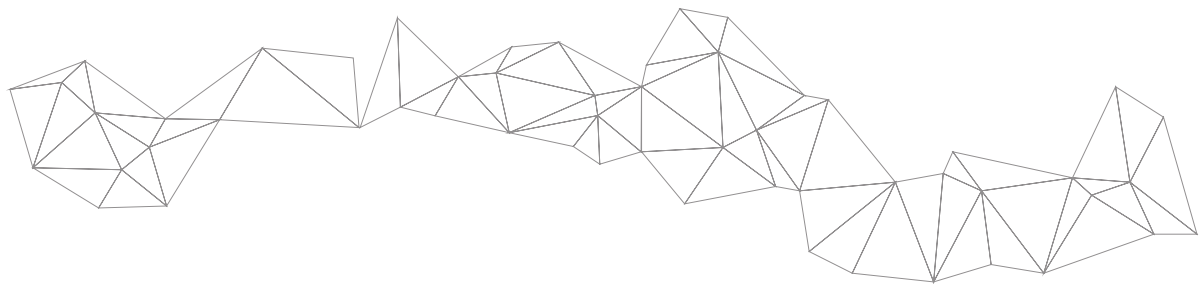
A prevalence of rickets in children that is higher than 1% has been suggested to warrant a public health response, to assess the global prevalence and disease burden of vitamin D deficiency (104), but this may be challenging without clear definition and etiology.



**Table 2. Reported data on nutritional rickets in children and adolescents in some countries**

Country, year	Reported data	Population type	Age	Diagnostic method
Bangladesh, 2008 (73)	0.99%	Population sample (n = 20 000)	1–15 years	Clinical/radiographs
Canada, 1988–1993 (74)	17 cases in those of African-Asian origin	Hospital based	7–33 months	Radiographs/biochemical
Canada, 2002–2004 (40)	2.9 cases per 100 000	Canadian Paediatric Surveillance Program	0–18 years	Radiographs/biochemical
China, 1977–1983 (75)	40.7%	Population sample (n = 184 901)	<3 years	Clinical
China, 2003 (39)	41.6%	Population sample (n = 250)	12–24 months	Clinical
	3.7%			Clinical/biochemical/radiographs
China, 1994–1995 (76)	66% (46–85%)	Population sample (n = 1556)	24–84 months	Clinical
Congo, 2008 (77)	19.1% (florid) 15.5% (moderate) 14.2% (minimal)	Population sample (n = 301)	Not reported	Not specified
Denmark, 1995–2005 (78)	2.0 per 100 000 per year in local individuals and 100 per 100 000 per year in immigrants	Population (review of medical records)	0–2 years	Clinical
Ethiopia, 1965 (79)	42%	Hospital based	<5 years	Radiographs
Gambia, 2007 (37)	3.3% (radiographs+clinical signs) 3.7% (radiographs in combination with biochemical data)	Population sample (n = 6221)	0.5–17 years	Clinical
India, 2010 (80)	16.4%	Population sample (n = 111)	2.6 years (mean)	Clinical
India, 2011 (81)	30.3%	Population sample (n = 98)	2.5–3.5 months	Radiographs
India, 2012–2013 (82)	2.7 per 1000	Population sample (n = 16 274)	1–18 years	Radiographs
Iran, 1967–1973 (83)	15%	Hospital based	0–14 years	Radiographs
Japan, 2009 (84)	9 cases per 100 000 per year	Hospital based (84 pediatric departments)	0–4 years	Clinical
Jordan, 2001 (11)	10.6%	Hospital based (n = 443)	3–24 months	Clinical/ biochemical/radiographs
Kenya, 2014 (85)	57% in males 43% in females	Hospital based	0–5 years	Clinical
Malawi, 2016 (86)	47.6%	Population sample (n = 42)	3–15 years	Radiographs
Mongolia, 1997 (87)	72.3% (1 of 9 signs) 49.0% (2 of 9 signs)	Population sample (n = 441)	0–60 months	Clinical
Mongolia, 1999 (88)	32.1% (at least 1 sign)	Population sample (n = 4156)	<5 years	Clinical
Mongolia, 2001 (89)	24.0% (at least 2 signs)	Population sample (n = 932)	6–59 months	Clinical
Mongolia, 2010 (90, 91)	55.6% (1 of 8 signs) 47.8% (1 of 7 signs) 55% Total prevalence	Population sample (n = 705)	0–59 months	Clinical
New Zealand, 1998 (92)	18 reports of rickets (10 males and 8 females)	Hospital based	<5 years	Radiographs
New Zealand, 2010–2013 (93)	Annual incidence 2.2 per 100 000	Prospective surveillance	<15 years	Biochemical/radiographs
Nigeria, 1998 (94)	9.2%	Population sample (n = 218)	6–35 months	Clinical



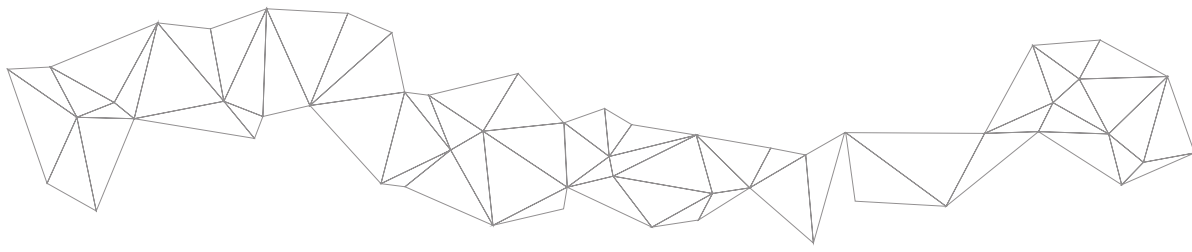


Country, year	Reported data	Population type	Age	Diagnostic method
Nigeria, 2012 (95)	1.2%	Intervention trial ( <i>n</i> = 647 enrolled, 390 completed 18-month follow-up)	12–18 months	Radiographs
Pakistan, 2014 (96)	27%	High schools ( <i>n</i> = 189)	11–16 years	Biochemical
Saudi Arabia, 1996–1997, (97)	68 per 100 000 26 per 100 000	Hospital based	10–15 years	Clinical (symptomatic) Radiographs
Republic of Korea, 2007–2009 (98)	14 cases	Hospital based ( <i>n</i> = 171)	0–24 months	Radiographs
Turkey, 1994 (99)	9.8%	Population sample	3–36 months	Clinical/biochemical
Turkey, 2002–2003 (12)	6.8%	Hospital based ( <i>n</i> = 305)	0–3 years	Clinical/biochemical/radiographs
Turkey, 2004–2009 (8)	3.1%	Hospital based ( <i>n</i> = 30 000 records reviewed, 946 with rickets)	4 months to 15 years	Clinical/diet/biochemical/radiographs
United Kingdom of Great Britain and Northern Ireland, 2000–2001 (100)	7.5 per 100 000 (white: 0.4 per 100 000 per year; South Asian 38 per 100 000 per year; black 95 per 100 000/year)	Sample of pediatricians ( <i>n</i> = 119)	<5 years	Biochemical/radiographs
United Kingdom of Great Britain and Northern Ireland, 2007–2011 (72)	4.78 per 100 000 (episode based) 3.16 per 100 000 (person based)	Hospital based (all hospital admissions in the United Kingdom of Great Britain and Northern Ireland)	<15 years	Based on International Classification of Diseases (ICD) codes for active rickets
United States of America, 1986–2003 (101)	166 cases reported	Review of 22 publications	4–54 months	Clinical/biochemical/radiographs
United States of America, 2001–2010 (102)	2.23 per 100 000 per year (rickets-associated hospitalization rate)	Patient Information Reporting System (retrospective)	<10 years	Based on the 9th ICD codes for rickets
United States, of America, 1970–2009 (71)	0 per 100 000 in 1970 2.2 per 100 000 in 1980 3.7 per 100 000 in 1990 24.1 per 100 000 for 2000	Rochester Epidemiology Project data (data from health-care facilities)	<3 years	Radiographs
Yemen, 1987 (103)	27%	Vaccination clinic	<5 years	Not reported





## **Understanding the diverse causes or determinants of nutritional rickets**



## Vitamin D status

Vitamin D is a fat-soluble precursor of the steroid hormone 1,25-dihydroxycholecalciferol (1,25(OH)<sub>2</sub>D or vitamin D<sub>3</sub>). In the skin, vitamin D<sub>3</sub> is formed in two steps, from 7-dehydrocholesterol into previtamin D and then into vitamin D<sub>3</sub> upon exposure of skin cells to ultraviolet (UV) radiation from sunlight (105) and subsequent conversion to pro-vitamin D (106, 107). In temperate climates, this only occurs during the summer months; at tropical latitudes, UVB at the appropriate wavelength is present year-round. Vitamin D is also obtained from certain foods as vitamin D<sub>3</sub> (animal sources) or vitamin D<sub>2</sub> (plant sources), and in small quantities as 25(OH)D. Independent of the source (skin production or consumed from foods), vitamin D is metabolized (hydroxylated) in the liver by 25-hydroxylase, to produce 25(OH)D (also called calcidiol). Therefore, the level of 25(OH)D in the body reflects both vitamin D intake and its endogenous production from sunlight (108). It is further metabolized into its active form, 1,25(OH)<sub>2</sub>D, also referred to as calcitriol) in the kidneys for systemic actions, and in many organs and tissues, for mainly local effects (auto and paracrine actions) (109). Plasma 25(OH)D is considered to be the main bodily pool of vitamin D, but both 25(OH)D and vitamin D<sub>3</sub> may be present in fat and muscle tissue. The availability of these pools is unclear. The levels of 25(OH)D mainly depend on supply (sun exposure and intake), while 1,25(OH)<sub>2</sub>D is under strict hormonal control.

The main function of active vitamin D is to promote intestinal absorption of calcium and phosphate and, jointly with other hormones, to stimulate their renal reabsorption. Vitamin D also helps to maintain plasma calcium and phosphate at adequate levels to promote bone mineralization. At the same time, vitamin D can help restore serum calcium and phosphate levels when they are low, by stimulating bone resorption in conjunction with PTH (110, 111).

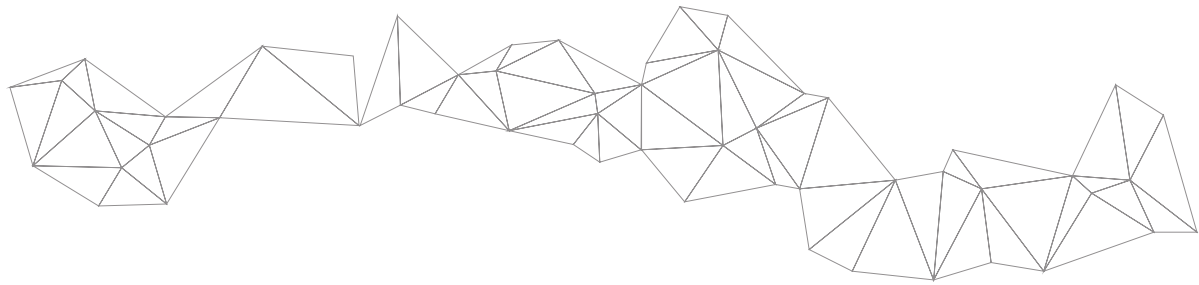
As vitamin D receptors are present in many different cells in the body, vitamin D is involved in many other non-osseous and calcitropic functions, such as in neuromuscular functions and modulation of the immune system and inflammation (112–114). These functions occur by modulating the transcription of cell-cycle proteins of vitamin D receptors on target cells. Active vitamin D interacts with its nuclear receptor, the vitamin D receptor, and this complex then binds to a specific vitamin D-responsive element and transcription factors. This process leads to the transcription of mRNAs, which code for calcium-transporting proteins, bone matrix proteins, or cell-cycle-regulating proteins (108).

There are only a few foods that are naturally rich in vitamin D, such as fatty fish and fish liver oils. Vitamin D is found in other foods, such as in beef liver, cheese and egg yolks, but only in small quantities. In some countries, certain foods are mandatorily or voluntarily fortified with vitamin D. With infant formula milk, vitamin D fortification is strictly controlled, with higher levels than in breast milk and other milk sources because of its lower bioavailability.

Either vitamin D<sub>2</sub> or vitamin D<sub>3</sub> may be added to foods but both interact with minerals and both degrade in the presence of moisture and oxygen (115). Commercially, a dry-stabilized form of the vitamin is generally used in food fortification, which contains an antioxidant to protect the vitamin in the presence of minerals. Fortification practices vary from country to country but the most common foods fortified with vitamin D are milk and other dairy products, including dried milk powder, evaporated milk, margarines (116) and vegetable oils (117).

### Assessing vitamin D status

Diverse biomarkers of vitamin D status have been proposed. The most widely accepted and used marker is the plasma concentration of 25(OH)D. It is a biomarker of exposure to vitamin D from both cutaneous synthesis and dietary intake from food and supplements (117). This biomarker is used by most governmental public health advisory panels to base recommendations for the population intakes of vitamin D. Plasma or serum 25(OH)D concentration is stable throughout the day and has a relatively long circulating half-life of 15 days (118, 119). Samples can be obtained in fasting and non-fasting states and blood samples do not require immediate



processing. Although 25(OH)D concentrations may decrease with concurrent inflammation (120), they are considered within the normal variations of disease state. Plasma 25(OH)D can be measured using a variety of assays (e.g. radioimmunoassay, high-performance liquid chromatography, liquid chromatography–tandem mass spectrometry [LC-MS]).

There are variations in results between assays and between laboratories. To improve the standardization of 25(OH)D assays, the Office of Dietary Supplements of the National Institutes of Health established the Vitamin D Standardization Program, in the USA in 2010. This programme provides participating laboratories with one-time sets of 40 different reference materials for bias assessment and calibration, as well as 40 blinded samples per year with assigned values measured by a reference LC-MS method for both 25(OH)D<sub>2</sub> and 25(OH)D<sub>3</sub>, to certify analytical performance such as bias and imprecision (121). Over 20 laboratories and assay manufacturers are currently participating in this programme (122). Additionally, the Vitamin D External Quality Assessment Scheme, from the Charing Cross Hospital, UK, provides participating laboratories with 20 samples per year that have reference values for 25(OH)D<sub>2</sub> and 25(OH)D<sub>3</sub>, for assessment of bias (123) and to allow for inter-assay and between-laboratory comparisons.

There is no international consensus on the thresholds of serum 25(OH)D to classify vitamin D nutritional status.

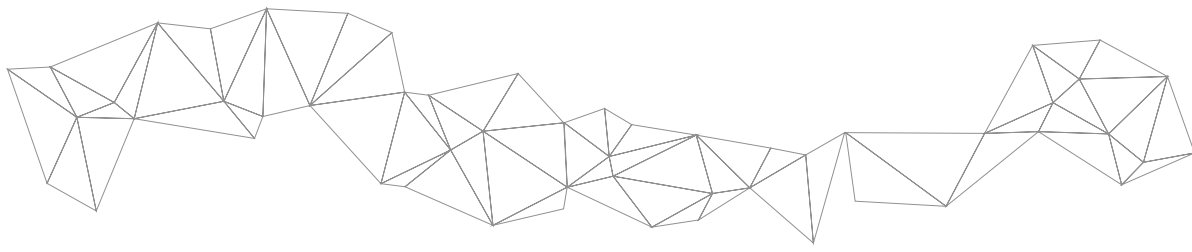
The Scientific Advisory Committee on Nutrition (SACN) for the UK recommended that individuals at the population level in the UK should not have serum 25(OH)D concentrations below 25 nmol/L at any time of the year, in order to protect musculoskeletal health (124). The Institute of Medicine (IOM) programme unit of the National Academies (now called the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine [the National Academies]), in the USA established their recommendations at the population level, based on preventing concentrations below 30 nmol/L for musculoskeletal outcomes, and have stated that for other health outcomes there is currently too little evidence on which to base a recommendation (125). This value was revised and accepted by other experts in 2018 (104). The Endocrine Society, a global organization representing professionals in the field of endocrinology and aimed at patient groups, defines vitamin D deficiency as 25(OH)D concentrations below 50 nmol/L and vitamin D insufficiency as 52.0–72.5 nmol/L, based on multiple health outcomes, including but not limited to musculoskeletal outcomes (126). Similar cut-off points have been suggested by the European Food Safety Authority (EFSA) (127).

A proposed classification for serum 25(OH)D levels in the context of skeletal mineralization and mineral ion metabolism for the prevention of nutritional rickets has been proposed by a group of experts (4):

- sufficiency: >50 nmol/L (>20 ng/mL);
- insufficiency: 30–50 nmol/L (12–20 ng/mL);
- deficiency: <30 nmol/L (<12 ng/mL).

Among healthy individuals, the recommended nutrient intake of vitamin D is 200 IU/day (5 µg/day) for infants, children and adolescents, based on the Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Consultation on Human Vitamin and Mineral Requirements to prevent rickets (128). The WHO report on the [Global burden of disease from solar ultraviolet radiation](#) reported that a level of 10 nmol/L (4 ng/mL) is the level likely to be associated with frank disease (clinical diagnosis of rickets or osteomalacia) (129).

There is no global WHO guideline at this time on 25(OH)D levels below 25–30 nmol/L being associated with an increased risk of rickets. The use and interpretation of biomarkers and their concentrations for assessing vitamin D nutritional status and assessing risk of rickets in individuals and populations is a critical topic and lacks international consensus.



## **Factors that affect vitamin D status**

### ***Sun exposure***

Season, geographic latitude and altitude, time of day, cloud cover, smog or pollution, the amount of melanin in the skin, use of sun screen, covering of skin for cultural reasons, and avoidance of outdoor activities are factors that affect exposure to UV radiation and synthesis of vitamin D (130). The UV energy above a latitude of 42 degrees north is insufficient for the synthesis of vitamin D through the skin during the winter months (46). The UV energy below a latitude of 34 degrees north allows skin production of vitamin D throughout the year, upon exposure of the skin to the UV light.

### ***Poor nutrition***

Since only limited foods are naturally rich sources of vitamin D and only a few foods are fortified with vitamin D worldwide (and with insufficient coverage), low vitamin D intake is commonly found. In populations with low intake of dairy products, which are fortified with vitamin D in several countries, low vitamin D status is common (125).

### ***Age***

Infants who are exclusively breastfed rely on a single source of food for all their nutrition. As such, they are in a critical and potentially vulnerable period, owing to the rapidly growing skeleton. Nevertheless, human milk is species specific, and its nutrients are secreted as bound components, with vitamin D, for instance, bound to the protein portion then later to the fat portion of the milk (132, 133). WHO recommends that very low-weight infants be given vitamin D supplements at a dose ranging from 400 IU to 1000 IU per day until 6 months of age (134). In susceptible populations, prolonged exclusive breastfeeding without the use of vitamin D supplements may be associated with an increased risk of nutritional rickets (135–137). Provision of vitamin D supplementation to the lactating mother during the breastfeeding period positively correlates with the vitamin D concentrations in the infants if very high doses of vitamin D are given (138). Infants are also at risk of vitamin D deficiency if born during the winter, or born to mothers who were vitamin D deficient during pregnancy. Similarly, adolescents have high metabolic demands for vitamin D, owing to the rapid growth of the skeleton during puberty (139), and are therefore at higher risk of vitamin D deficiency. As people age, the skin cannot synthesize vitamin D efficiently, and the kidneys are less able to convert vitamin D to its active form (140).

### ***Skin type***

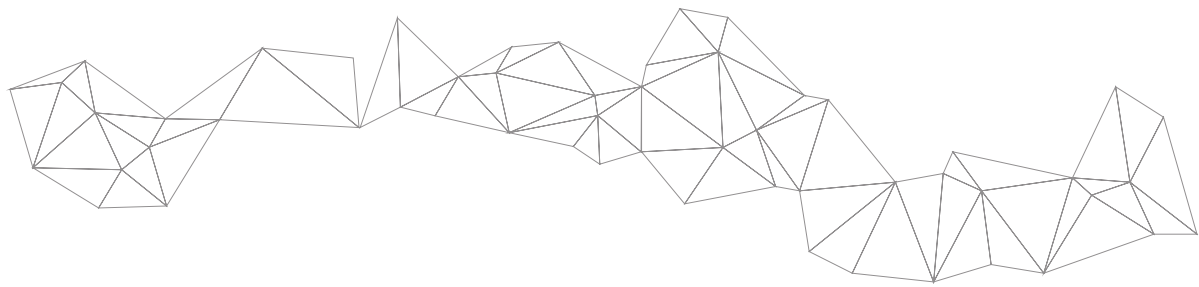
People with the greatest amount of melanin (dark skin) have a reduced ability to produce vitamin D from exposure to sunlight (141). Individuals with dark-coloured skin synthesize less vitamin D on exposure to sunlight than those with light-coloured skin (142).

### ***Obesity***

Obese individuals have low serum levels of 25(OH)D (143). There are several postulated reasons for this, such as less outdoor activity or more cover-up and therefore avoidance of sun exposure; alterations in the vitamin D endocrine system; higher production of 1,25(OH)<sub>2</sub>D, which exerts negative feedback control on the hepatic synthesis of serum 25(OH)D; and metabolic clearance due to enhanced uptake by adipose tissue, volumetric dilution, and decreased bioavailability of vitamin D from cutaneous and dietary sources because of its deposition in body fat compartments (144).

### ***Poor absorption of fat***

Vitamin D is liposoluble, so it requires some dietary fat in the intestine for its absorption. Individuals who have less ability to absorb dietary fat may require extra vitamin D (145). The poor absorption of fat is associated



with a variety of medical conditions, including pancreatic enzyme deficiency, Crohn disease, cystic fibrosis, coeliac disease, surgical removal of any part of the stomach or intestines, and some forms of liver disease (19).

### **The prevalence of hypovitaminosis D**

Low vitamin D status (measured by biochemical parameters) appear to be highly prevalent worldwide in infants, children, adolescents and pregnant women (146).

Nonetheless, there are very limited population-representative data in large parts of the world. Some reviews of available data, although with methodological limitations, have shown major regional differences in the prevalence low concentrations of vitamin D biomarkers (146, 147).

Because of the lack of international consensus on the most appropriate cut-off values for 25(OH)D to define vitamin D status, a variety of values are typically presented. Table 3 shows the prevalence of low 25(OH)D concentrations, as reported in surveys of children aged less than 5 years, that are representative of the national, regional (subnational) or first administrative (e.g. canton, province) level. The prevalence of vitamin D concentrations below about 25 nmol/L and 50 nmol/L varies widely, depending on the population assessed. A relatively low prevalence (20–25%) of 25(OH)D concentrations below 50 nmol/L is reported in Argentina, Jordan, Mexico, Thailand (rural population) and the USA; a moderate prevalence (26–50%) is reported in Indonesia, Iran, Malaysia (urban population), Mongolia, Pakistan, Tajikistan and Thailand (urban population); and a very high prevalence (>60%) is reported in Afghanistan. Table 4 shows the prevalence of vitamin D deficiency among school-age children and adolescents from nationally representative surveys in some countries. The prevalence of 25(OH)D concentrations below 25–30 nmol/L varied between school-age children (5–12 years) to 56% in Iranian children and adolescents (5–18 years) in winter. The prevalence of 25(OH)D concentrations below 50 nmol/L also varied from 10% in Mexican school-age children (6–12 years) to 93% in Iranian children and adolescents (5–18 years) in winter. In women aged 15–49 years, the prevalence of serum 25(OH)D concentrations below 20–30 nmol/L ranged from less than 10% in countries such as Australia, Canada and France to over 50% in countries such as Afghanistan, Iraq, Jordan and Mongolia (see Table 5).

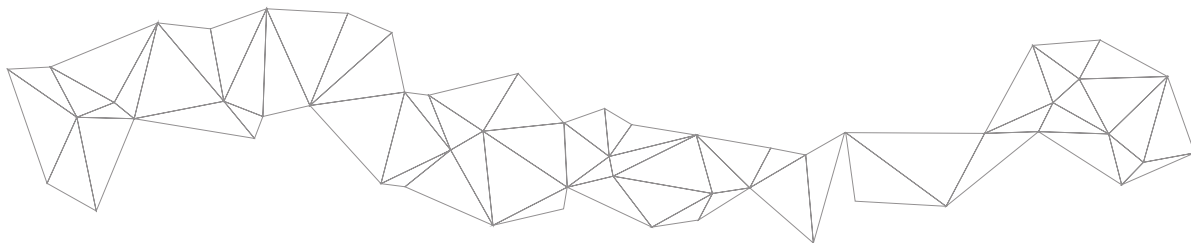
The cutaneous production of vitamin D may be lower among adolescent girls and women in settings where it is the cultural norm to wear clothes that cover most of the skin (128).

### **Causes of vitamin D deficiency-related rickets**

Lack of sunlight was identified as a risk factor for rickets as early as 1822, but it was not until 100 years later that vitamin D deficiency was linked to rickets (180). Depending on the age, causes of nutritional rickets vary.

Most cases of rickets in infants that are attributable to vitamin D deficiency are related to low sun exposure (181, 182) and excessive skin coverage (183) but also to maternal vitamin D deficiency (42, 181, 184), prolonged exclusive breastfeeding, particularly among dark-skinned infants (7, 40, 64, 71, 101, 185), or malnutrition (102). A higher prevalence of nutritional rickets has been reported among breastfed infants from different countries (71, 186), such as in Greece (187), Nigeria (188), Pakistan (189), and among dark-skinned children in Canada (40) and in the USA (71, 135), compared to non-breastfed infants. It is important to note that exclusive breastfeeding has been associated with nutritional rickets only among older infants (135, 136), particularly those not receiving vitamin D supplements (145), but not among infants under 6 months of age with low vitamin D status (190).

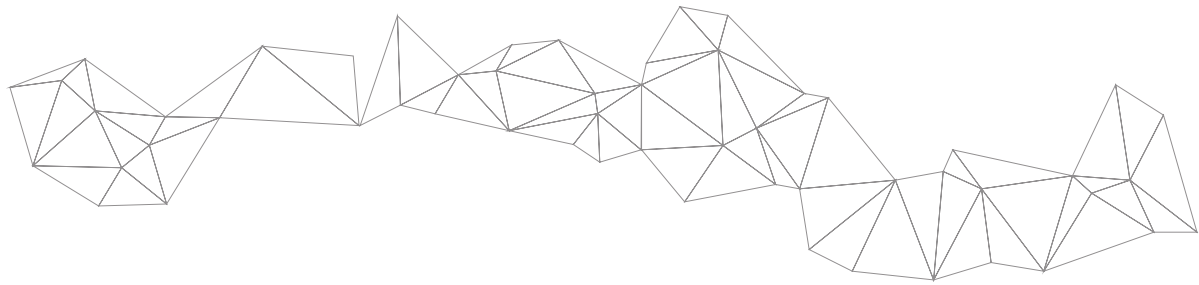
In adolescents, the diagnosis of rickets may be difficult, as its presentation could be subtle and nonspecific. Cases of rickets among adolescents have been related to dark skin, low intake of calcium and vitamin D, lack of sunlight, use of hijab or niqab, and being female (6, 191–193). Rickets in adolescents has been reported in India (194), the United Arab Emirates (195) and Iran (196, 197).



**Table 3. Vitamin D status of children aged <5 years, based on serum/plasma 25(OH)D samples collected in representative<sup>a</sup> surveys worldwide**

Country, year	Age range	Sample size	Season	Prevalence of vitamin D deficiency (%)	Cut-off point used (nmol/L)	25(OH)D assay method
Afghanistan, 2013 (148)	6–59 months	N/S	June–October	17%	<20 nmol/L	No data available
				64%	20–49 nmol/L	
Argentina, 2004–2005 (149)	6–23 months	N/S	October–December	3%	<27.5 nmol/L	Radioimmunoassay
				21%	27.5–49 nmol/L	
Cambodia, 2014 (150)	6–71 months	775	June–December	15%	<50 nmol/L	(Electro)chemiluminescence immunoassay
Canada, 2009–2011 (151)	3–5 years	N/S	AYR	11%	<50 nmol/L	Chemiluminescence immunoassay
Indonesia, 2011 (152, 153)	2–4 years	N/S <sup>b</sup>	AYR	0%	<25 nmol/L	Enzyme-linked immunoassay
				35% urban 43% rural	<50 nmol/L	
Iran, 2001 (154)	15–23 months	4013	May–June	3%	<25 nmol/L	High-performance liquid chromatography
				36%	<50 nmol/L	
Jordan, 2010 (155)	12–59 months	915	March–April	20%	<27.5 nmol/L	Liquid chromatography-tandem mass spectrometry
Malaysia, 2010–2011 (152, 156)	4–6 years	N/S <sup>c</sup>	May–October	35% urban 18% rural	<50 nmol/L	Chemiluminescence immunoassay
Mexico, 2005–2006 (157)	2–5 years	366	October–May	<1%	<20 nmol/l	Enzyme-linked immunosorbent assay
				25%	<50 nmol/l	
Mongolia, regional, 2001 (89)	6–59 months	405	June	3%	<25 nmol/L	Radioimmunoassay
Mongolia, 2004 (158)	6–59 months	388	May–June	41%	<25 nmol/L	Ferment immune method (microboard)
Mongolia, 2010 (90)	6–59 months	524	July–September	42%	<23 nmol/L	Enzyme-linked immunoassay
Pakistan, 2011 (159)	0–59 months	N/S	January–June	9%	<20 nmol/L	Not specified
				40%	<50 nmol/L	
Tajikistan, 2009 (160)	6–24 months	625	October	14%	<25 nmol/L	Enzyme-linked immunoassay
				40%	<50 nmol/L	
Tajikistan, 2016 (161)	3–5 years	178	January–August	31% urban 25% rural	<50 nmol/l	Chemiluminescence immunoassay
Thailand, 2011 (152, 162)	1.5–3 years	42	AYR	8%	<25 nmol/L	Chemiluminescence immunoassay

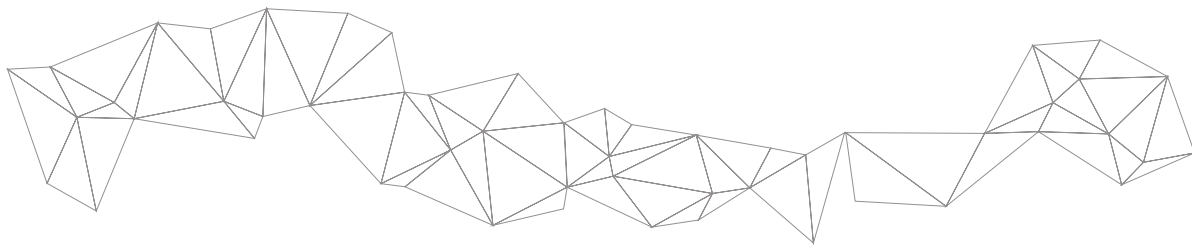




Country, year	Age range	Sample size	Season	Prevalence of vitamin D deficiency (%)	Cut-off point used (nmol/L)	25(OH)D assay method
United Kingdom of Great Britain and Northern Ireland, 1997 (163)	4–6 years	76 females 73 males	AYR	2% females 3% males	<25 nmol/L	Radioimmunoassay
				25% females 23% males	<50 nmol/L	
United Kingdom of Great Britain and Northern Ireland, 2008–2012 (164)	1.5–3 years	42	AYR	8%	<25 nmol/L	Chemiluminescence immunoassay
United Kingdom of Great Britain and Northern Ireland, 2011 (165)	5–11 months	166	January–August	6%	<25 nmol/L	Chemiluminescence immunoassay
	12–18 months	300		2%	<25 nmol/L	
				15% (15% boys, 15% girls); 8% white, 34% black, 18% hispanic, 21% other)	<50 nmol/L (<20 ng/mL)	
			63% (61% boys, 66% girls); 54% white, 85% black, 73% hispanic, 62% other)	<75 nmol/L (<30 ng/mL)		
United States of America, 2003–2006 (166)	1–5 years	1799	AYR	1% (1% boys, 1% girls); 0% white, 3% black, 1% hispanic, 1% other)	<25 nmol/L (<10 ng/mL)	Radioimmunoassay

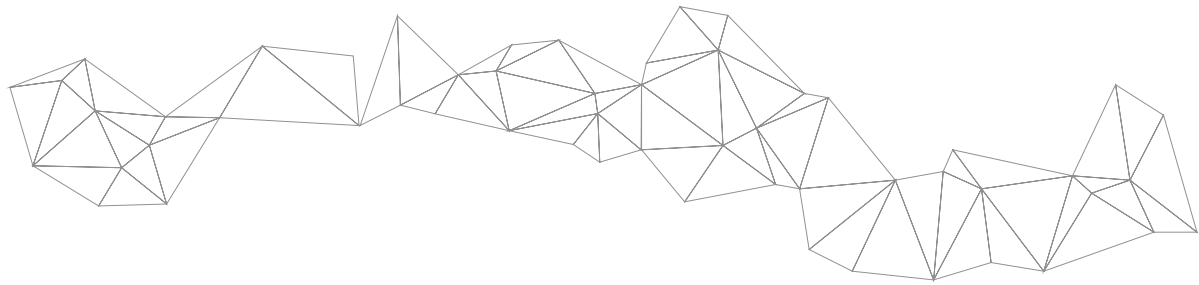
AYR: all year round; N/R: not reported; N/S: not specified; 25(OH)D: 25-hydroxycholecalciferol.

- <sup>a</sup> All surveys are nationally representative, household-based, cross-sectional surveys, except for those indicated as follows: Argentina (representative of the Patagonia region), Mongolia, 2001 (regional, dzud affected and unaffected areas within country).
- <sup>b</sup> Vitamin D status was determined in a relatively small ( $n = 276$ ) sample of children aged 2–12 years in this study. Sample size was not reported for children aged 2–4 years of age. Results should be interpreted with caution.
- <sup>c</sup> Vitamin D status was determined in 861 children aged 4–12 years of age in this study. The sample size was not reported for children aged 4–6 years.



**Table 4. Vitamin D status of school-age children and adolescents based on serum/plasma 25(OH)D samples collected in representative<sup>a</sup> surveys worldwide**

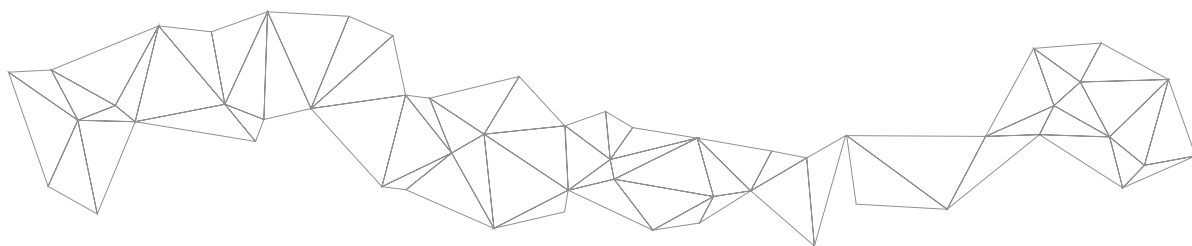
Country, year	Age range	Sample size	Season	Prevalence of vitamin D deficiency (as defined by assessors)	Cut-off point used	25(OH)D assay method
Australia, 2011–2012 (167)	12–17 years	839	AYR	3%	<30 nmol/L	Liquid chromatography–tandem mass spectrometry
				15%	<50 nmol/L	
Austria, 2010–2012 (168)	7–14 years	364	AYR	22% females 18% males	<25 nmol/L	High-performance liquid chromatography
				62% females 56% males	<50 nmol/L	
Canada, 2007–2009 (169)	6–11 years	903	AYR	14%	<50 nmol/L	Chemiluminescence immunoassay
	12–19 years	945		5%	<27.5 nmo/L	
				26%	<50 nmol/L	
Canada, 2009–2011 (151)	6–11 years	N/S	AYR	24%	<50 nmol/L	Chemiluminescence immunoassay
	12–19 years	N/S		29%	<50 nmol/L	
China, 2010–2012 (170)	6–11 years	7037	AYR	6%	<25 nmol/L	Radioimmunoassay
				47%	<50 nmol/L	
	12–14 years 15–17 years	3928 3508		9% 58%	<25 nmol/L <50 nmol/L	
Indonesia, 2011 (152, 153)	5–12 years	N/S <sup>b</sup>	AYR	0%	<25 nmol/L	Enzyme-linked immunoassay
				47% urban 45% rural	<50 nmol/L <50 nmol/L	
Iran, 2013 (171)	5–18 years	667	Winter (January, February)	56%	<25 nmol/L	Enzyme-linked immunoassay
				93%	<50 nmol/L	
Malaysia, 2010–2011 (152, 156)	7–12 years	N/S <sup>c</sup>	May–October	57% urban 46% rural	<50 nmol/L	Chemiluminescence immunoassay
Mexico, 2005–2006 (157)	6–12 years	659	October–May	<1%	<20 nmol/L	Enzyme-linked immunosorbent assay commercial kit
				10%	<50 nmol/L	
Thailand, 2011 (152, 162)	6–12 years	318	January–August	52% urban 29% rural	<50 nmol/L	Chemiluminescence immunoassay



Country, year	Age range	Sample size	Season	Prevalence of vitamin D deficiency (as defined by assessors)	Cut-off point used	25(OH)D assay method
United Kingdom of Great Britain and Northern Ireland, 2008–2012 (164)	4–10 years	237	AYR	14%	<25 nmol/L	Chemiluminescence immunoassay
	11–18 years	523		22%		
United Kingdom of Great Britain and Northern Ireland, 1997 (163)	7–10 years	133 females 167 males	AYR	7% females 4% males	<25 nmol/L	Radioimmunoassay
				26% females 26% males	<50 nmol/L	
	11–14 years	164 females 177 males		11% females 11% males	<25 nmol/L	
	15–18 years	162 females 153 males		44% females 40% males	<50 nmol/L	
				10% females 16% males	<25 nmol/L	
			49% females 54% males	<50 nmol/L		
United States of America, 2003–2006 (166)	6–11 years	1768		1.8%	<30 nmol/L	Radioimmunoassay

AYR: all year round; N/S: not specified; 25(OH)D: 25-hydroxycholecalciferol.

- <sup>a</sup> All surveys are nationally representative, household-based, cross-sectional surveys, except for those indicated as follows: the Viet Nam 2011 survey was a facility-based survey of school-age children.
- <sup>b</sup> Vitamin D status was determined in a relatively small ( $n = 276$ ) sample of children aged 2–12 years in this study. Sample size was not reported for children aged 5–12 years. Results should be interpreted with caution.
- <sup>c</sup> Vitamin D status was determined in 861 children aged 4–12 years in this study. The sample size was not reported for children aged 7–12 years.

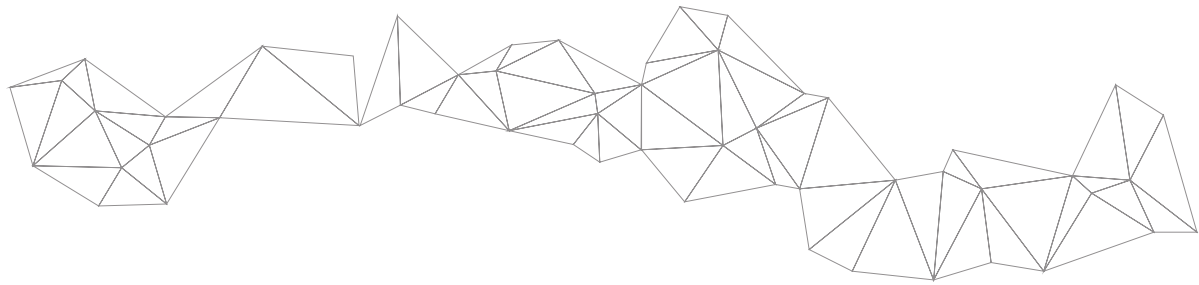


**Table 5. Vitamin D status of women aged 15–49 years based on serum/plasma 25(OH)D samples collected in representative<sup>a</sup> surveys worldwide**

Country, year	Group, age range	Sample size	Season	Prevalence of vitamin D deficiency	Cut-off point used	25(OH)D assay method
Afghanistan, 2013 (148)	Women, 15–49 years	1190	June–October	65%	<20 nmol/l	Not reported
				96%	<50 nmol/l	
Australia, 2011–2012 (167)	Women, 16–44 years	2099	AYR	9%	<30 nmol/L	Liquid chromatography–tandem mass spectrometry
				25%	<50 nmol/L	
Belgium, 2010–2011 (172)	Pregnant women, 15–45 years	1300	AYR	12%	<25 nmol/L	Radioimmunoassay
				45%	<50 nmol/L	
Cambodia, 2014 (150)	Women, 15–49 years	739	June–December	31%	<50 nmol/L	(Electro)chemiluminescence immunoassay
Canada, 2007–2009 (169)	Women, 20–39 years	650	AYR	3%	<27.5 nmol/L	Chemiluminescence immunoassay
				26%	<50 nmol/L	
China, 2010–2012 (173)	Pregnant women	1027	AYR	74%	<50 nmol/L	Radioimmunoassay
France, 2006–2007 (174)	Women, 18–29 years	N/S	AYR	7%	<25 nmol/L	Radioimmunoassay
				48%	<50 nmol/L	
Iraq, 2011–2012 (175)	Non-pregnant women, 15–49 years	776	December–March	75%	<30 nmol/L	Liquid chromatography–tandem mass spectrometry
				98%	<50 nmol/L	
Jordan, 2010 (155)	Non-pregnant women, 15–49 years	2032	March–April	60%	<30 nmol/L	Liquid chromatography–tandem mass spectrometry
Mexico, 2012 (176)	Women, 20–49 years	4162	AYR	37%	<50 nmol/L	Chemiluminescence immunoassay
Mongolia, 2010 (90)	Non-pregnant women, 15–49 years	867	July–September	52%	<23 nmol/L	Enzyme-linked immunoassay
Pakistan, 2011 (159)	Non-pregnant women, 15–49 years	N/S	January–June	67%	<50 nmol/L	Not reported
				25%	<20 nmol/L	
	Pregnant women, 15–49 years	N/S	69%	<50 nmol/L		
Philippines, 2013–2014 (177)	Women, 20–39 years	320	June–April	32%	<50 nmol/L	Chemiluminescence immunoassay
United Kingdom of Great Britain and Northern Ireland 2000–2001 (178)	Adults 19–64 years	1347	AYR	14% (men) 15% (women)	<25.0 nmol/L	Radioimmunoassay
United States of America, 2001–2006 (179)	Pregnant women, 13–44 years	928	AYR	33%	<50 nmol/L	Radioimmunoassay
	Non-pregnant women, 13–44 years	5173	AYR	42%	<50 nmol/L	

AYR: all year round; N/S: not specified; 25(OH)D: 25-hydroxycholecalciferol.

<sup>a</sup> All surveys are nationally representative, household-based, cross-sectional surveys, except for the Philippines 2013–2014 that was only conducted at a first administrative level (National Capital Region).



### Other causes of vitamin D-related rickets

As transplacental transmission of vitamin D predominantly happens during the third trimester of pregnancy, preterm infants are at higher risk of vitamin D deficiency (198). Vitamin D-deficient rickets can also result from perturbations in vitamin D metabolism (4). This could be the result of malabsorption disorders or as a result of genetic mutations. Specifically, a mutation in the CYP27B1 gene leads to deficiency of renal 1 $\alpha$ -hydroxylase enzyme, which is the final step in the activation of vitamin D, leading to low or undetectable levels of 1,25(OH)<sub>2</sub>D (28). This type of rickets is often referred as to type I vitamin D-dependent rickets (VDDR-I) (19). In addition, mutations in the vitamin D receptor (VDR) gene can lead to rickets, owing to resistance to the biological actions of 1,25(OH)<sub>2</sub>D, despite high levels of 25(OH)D (28). This type of rickets is often referred as to type II vitamin D-resistant rickets (19).

### Recommendations for vitamin D levels

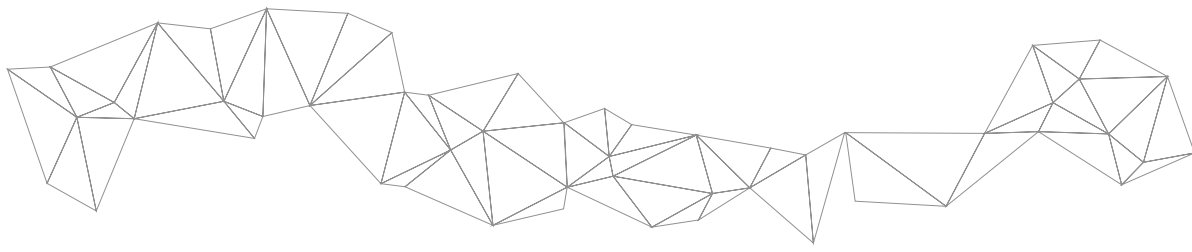
Serum 25(OH)D concentrations above 25–30 nmol/L have been considered by some to be the level necessary for ensuring normal bone health (128). The intake of vitamin D needed for each population group to achieve serum 25(OH)D concentrations above 25–30 nmol/L was then rounded to the nearest 50 IU and doubled to cover the needs of all individuals within that group, irrespective of the amount of exposure to sunlight. The resulting values were termed “adequate intake”. In 1998, WHO and FAO adopted this methodology in establishing the recommended nutrient intake (RNI) for vitamin D and defined 200 IU/day (5  $\mu$ g/day) as the RNI for infants, children and adolescents (128).

In 1997, this method was used by the Food and Nutrition Board of the IOM in the USA, to establish adequate intakes of vitamin D (199). In 2011, the IOM concluded that individuals are at risk of vitamin D deficiency at serum 25(OH)D concentrations below 30 nmol/L, and at risk for inadequacy at levels ranging from 30 nmol/L to 50 nmol/L (125). Further, they considered that practically all individuals would be sufficient at serum 25(OH)D levels  $\geq$ 50 nmol/L, such that 50 nmol/L is the serum 25(OH)D level that covers the needs of 97.5% of the population. Based on modelling the average vitamin D intakes required to attain 50 nmol/L, this organization established an estimated average requirement of 400 IU/day (10  $\mu$ g/day) and a recommended daily allowance (RDA) of 600 IU/day (15  $\mu$ g/day) for infants, children and adolescents in the USA. In 2016, the SACN (UK) defined the RNI as 10  $\mu$ g/day (124), which is the same level recommended by the Nordic Nutrition Recommendations (NNR), EFSA and DACH (the joint committee for nutritional recommendations in Germany, Austria and Switzerland) (127, 200, 201). In contrast, Australia and New Zealand established their recommendations at 5  $\mu$ g/day (202) and Japan established a range of 2.5–5.5  $\mu$ g/day (203). Most of these recommendations were established acknowledging that the contribution of sunshine-derived vitamin D is difficult to assess and that, therefore, recommendations for sun exposure could not be formulated, so the recommendations took an approach of “minimal sunshine exposure”. However, the NNR considered some level of sun exposure but suggests an intake of 20  $\mu$ g/day if cutaneous synthesis is restricted. Japan also established their recommendations based on an adequate sun exposure. Both RNI and RDA are estimated requirements, owing to the lack of studies regarding the dose–response relationship in infants and children and the limitations in data on the prevention of rickets (as this cannot be tested in randomized controlled trial designs).

## Calcium status

### Overview of calcium metabolism and sources

Calcium constitutes 1–2% of the total body weight. About 99% of the body’s calcium is found in the bones and teeth as hydroxyapatite, providing rigidity to the skeleton. The other 1% is in blood, extracellular fluid, muscle and other tissues, and mediates various metabolic processes. Calcium is needed in children and adolescents for bone mineralization, a process that is particularly important at young ages (0–3 years) and during adolescence (11–14 years) (204). However, this process continues until young adulthood, with about 90% of the bone mass acquired by 17 years of age and 99% by 22 years (205). Calcium is also needed for other



essential functions, such as muscle contraction and nerve conduction. Natural dietary sources of calcium include dairy products, such as milk, cheese and yoghurt; nuts; certain vegetables, such as spinach, broccoli, kale, turnip and collard greens; and soybeans.

### **Data on low calcium intake in populations**

There are no good biochemical markers available to assess calcium adequacy; therefore, data rely on data available on calcium intake (206). Several methods to assess dietary intake (207) have been proposed (208, 209), with limitations. At population level, calcium intake can be estimated through various means, including dietary surveys using 24-hour recalls, food frequency questionnaires or food weighing, as well as through secondary data estimates derived from FAO food balance sheets or household consumption and expenditure surveys. In a systematic review of data from 74 countries, it was estimated that average national dietary calcium intake among adults ranged from 175 mg/day to 1233 mg/day, although many of the studies were not nationally representative of the general population of adults. Among pregnant women, the mean calcium intake has been estimated as 948.3 mg/day in high-income countries and 647.6 mg/day in low- and middle-income countries, using data from cross-sectional, cohort and intervention studies reporting calcium intake during pregnancy (210).

Low calcium intake has been reported as common worldwide; however, there are only a few countries with nationally representative data on calcium consumption.

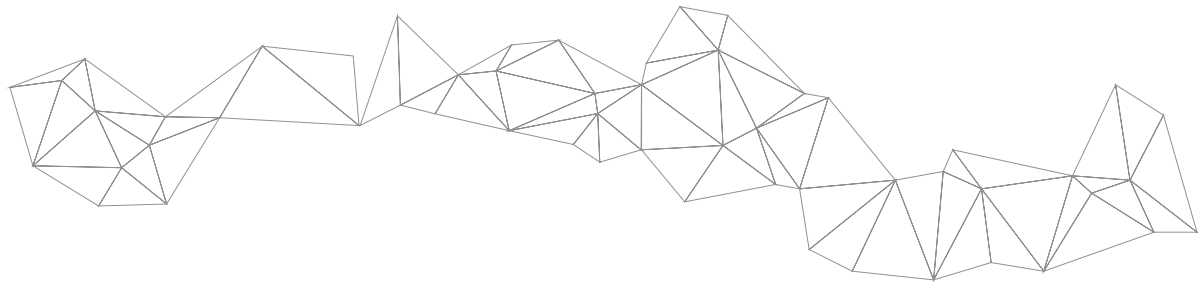
In Asia, data from the National Nutrition Surveys of China conducted in 1982, 1992 and 2002 show that the average calcium intake decreased from 695 mg/day in 1982 to 388 mg/day in 2002 (211). This occurred despite the consumption of dairy products but it was explained by a decrease in the intake of other foods rich in calcium, such as certain vegetables and grains. Data from rural areas in India, collected by the Indian National Nutrition Monitoring Bureau in 1975–79, 1988–90 and 1996–97, also showed a decrease in calcium intake from 606 mg/day in 1975–79 to 453 mg/day in 1996–97 (211). The 2011–2013 Korea National Health and Nutrition Examination Survey reported an average consumption of 534 mg/day of calcium among children aged 13 years and younger and 514 mg/day among adolescents aged 14–19 years (212). In Bangladesh, it was recently reported that the general population has low calcium intake, particularly among young children and women aged 15–49 years (213).

In Europe, the EFSA reported data from 13 dietary surveys in nine European Union countries in 2012 (Finland, France, Germany, Ireland, Italy, Latvia, the Netherlands, Sweden and the UK). The range of average calcium intake was 307–584 mg/day in infants, 533–838 mg/day in children aged 1–3 years, 589–986 mg/day in children aged 3–10 years, 675–1273 mg/day in children aged 10–18 years and 690–1122 mg/day in adults (214). In Russia, data from the available national surveys show that average calcium intake decreased from 688 mg/day to 567 mg/day between 1993 and 1996 (211).

In the Americas, data from the Continuing Survey of Food Intake and the National Health and Nutrition Examination Survey have found that calcium intake has not changed over time in the USA (215), with an average calcium intake in boys of 1008–1093 mg/day in those aged 1–13 years and 1296 mg/day in those aged 14–18 years, while in girls, average calcium intake was 977–988 mg/day in those aged 1–13 years and 918 mg/day in those aged 14–18 years in 2003–2006 (216). Data from the Mexican National Health and Nutrition Survey 2006 reported an average calcium intake of 887 mg/day and 740 mg/day in adolescent boys and girls, respectively (217), and 763 mg/day in school-age children (218).

### **Calcium bioavailability**

In general, calcium is a poorly absorbed nutrient, with most of the calcium consumed lost in faeces. Dairy products are good sources of calcium because of their high calcium content (about 300 mg of calcium per serving) and high bioavailability (about 32%) (219). The absorption of calcium from different dairy products and calcium-fortified foods is quite similar (220, 221). However, the bioavailability of calcium from certain



plant foods, such as spinach, is low, owing to the content of oxalate which forms insoluble salts with calcium and thus inhibits its absorption (222). On the other hand, low-oxalate vegetables, such as broccoli, kale and turnip collard greens, are highly bioavailable but their calcium content is low and one would need about 2–4 cups to obtain the amount of calcium found in 1 cup of milk (223). Phytate (wheat bran and unleavened bread) also greatly inhibits calcium absorption (224, 225) and foods with high phytate content, such as ready-to-eat breakfast cereals, are often fortified with calcium. Although soybeans contain oxalate and phytate, calcium absorption is very good (224). This is probably explained by the fact that soybeans are typically processed by the food industry into forms that are more easily digested, such as tofu (226). Calcium absorption in most supplements is similar to that of milk, but formulations containing citrate malate are better absorbed compared to other calcium supplements (227). Individuals that mainly consume plant-based diets and those who are lactose intolerant may be at risk of low calcium status.

### **Age**

Infants have very high rates of calcium absorption (60%), which subsequently decline to about 30% in childhood, with a slight rise in puberty to about 35%, then remain at 25% in adulthood and decline towards menopause (125). In pregnancy, rates of calcium absorption are doubled from the first trimester and continue to be high during the entire pregnancy (125).

### **Protein intake**

Protein intake stimulates acid release in the stomach, which increases calcium absorption; however, excess protein may also increase the excretion of urinary calcium (125).

### **Calcium excretion**

Aside from factors that affect calcium absorption, there are also factors that affect calcium excretion. For example, excessive dietary sodium leads to hypercalciuria, as sodium and calcium both share common reabsorption pathways in the renal tubules (228). A high-salt diet decreases body calcium retention compared to a diet that is low in salt (229). Caffeine and protein can also induce hypercalciuria, but to a much lesser extent, with some compensation during the day (222). This has become more important in recent years, owing to the consumption of caffeine-containing beverages such as soda and energy drinks.

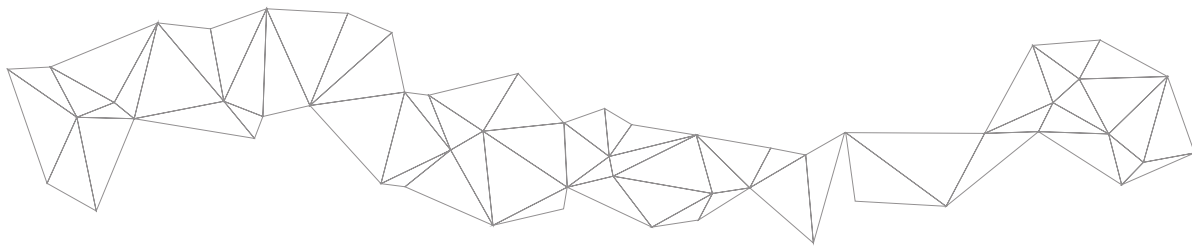
### **Recommendations for calcium intake**

There is no uniform criterion for setting calcium recommendations worldwide. Different methodologies, nomenclatures and age groups have been used. In addition, vitamin D intake and sun exposure may also alter calcium needs, as vitamin D is needed for absorption and retention of calcium (128). Therefore, recommendations from one country, based mostly on studies conducted in their populations, may not necessarily be applicable to another country with different dietary patterns, lifestyles and environments.

Recently, experts from different societies have proposed the use of the following classification of calcium intake for children aged 12 months and older (4), although this has not been endorsed by WHO:

- sufficient: >500 mg/day;
- insufficient: 300–500 mg/day;
- deficient: <300 mg/day.

FAO and WHO recommend 300–400 mg/day of calcium for infants, 500 mg/day in children aged 1–3 years, 600 mg/day in children aged 4–6 years, 700 mg/day in children aged 7–9 years and 1300 mg/day in children aged 9–18 years (128). WHO recognizes special situations in which calcium supplementation or higher levels may be needed. During pregnancy, among populations with low dietary calcium intake, calcium supplementation is recommended as part of routine antenatal care, to reduce the risk of pre-eclampsia (230).



The recommended dose is 1.5–2.0 g/day of oral elemental calcium, which should be divided into three doses (preferably taken at meal times). Very low-birth-weight infants receiving breast milk should be supplemented with calcium (120–140 mg/kg/day) and phosphorus (60–90 mg/kg/day) during the first months of life, to reduce the risk of metabolic bone disease (231).

### **Calcium intake in children with rickets**

Low calcium intake (below 300 mg/day), without vitamin D deficiency, could also result in rickets (3). Studies comparing calcium intake between children and adolescents with and without rickets have found significantly lower calcium intake among those with rickets (<300 mg/day) (213–217). Very low calcium intake (<300 mg/day) has been shown to increase the risk for developing rickets by almost 5-fold (213).

### **Other nutritional causes**

Rickets may also be caused by generalized poor nutrition or nutritional status, as these increase the risk of many nutrient deficiencies. In addition, the consumption of excessive amounts of fluoride (237) or heavy metals, such as strontium, aluminum and cadmium, which interfere with calcium and bone mineralization (5, 30, 238), may cause rickets. These minerals may be consumed from foods or drinking water (239).

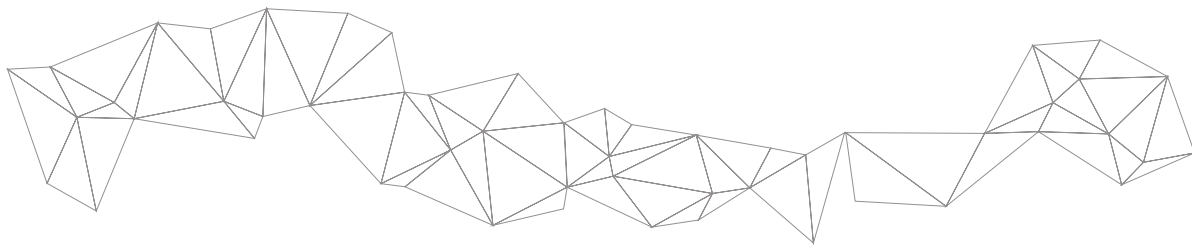
### **Preterm birth and low birth weight**

Preterm and low-birth-weight infants are at very high risk of metabolic bone disease, owing to the poor accretion of bone minerals, a process that occurs mainly during the last trimester of pregnancy. In addition, organ systems are immature and therefore the bioavailability of nutrients is low in these infants. This results in rickets of prematurity or osteopenia of prematurity. It has been reported that 55% of infants with very low birth weight (<1000 g) have rickets of prematurity (240). Retrospective cohort studies in different hospitals in the USA have found a high prevalence of rickets among all cases of infants with a low birth weight (31%) (241) and among infants with an extremely low birth weight (37%) (242). Similarly, a retrospective study in a hospital in Korea evaluating all cases of extremely low-birth-weight infants between 2004 and 2008 found that 44% had rickets (243). Other retrospective studies have also found a high prevalence of rickets among low-birth-weight infants in India (244), Ethiopia (245), Kenya (246) and Canada (247).





**Developing solutions or interventions that could prevent or mitigate nutritional rickets in infants, children and adolescents**



**P**ublic health interventions to prevent nutritional rickets must take into account a combination of screening for low vitamin D status and inadequate calcium intake, and appropriate intake of vitamin D and calcium, either by fortifying foods or by direct supplementation. In many locations, fortification of foods, such as milk in Canada and the USA, has proved to be a prudent public health measure (115). Vitamin D-deficiency rickets has been shown to be preventable with adequate intake of vitamin D through public health interventions (7). In addition, appropriate exposure to sunlight (based on skin type) is often included in guidelines; however, there are very limited studies testing the effects of sunlight on preventing (248) or treating rickets (249).

## Screening

### Risk assessment of vitamin D deficiency and low calcium intake

Obtaining a health history and evaluating dietary patterns could be used to screen children at risk for nutritional rickets, as part of routine antenatal and postnatal care visits with health-care professionals. However, there are currently no validated tools or questionnaires for this purpose.

A clinical history for infants may include the following questions:

- a. How long has/was your infant exclusively breastfed?
- b. If the answer is longer than 6 months, then ask whether the mother is providing vitamin D supplements.
- c. If the answer is negative, also ask whether the infant is consuming foods fortified with vitamin D.
- d. Is your child exposed to the sun? Does he/she play outside with skin exposed?
- e. Does your child use vitamin D supplement?

If answers to both b and c are negative, then this infant may be at risk of vitamin D deficiency.

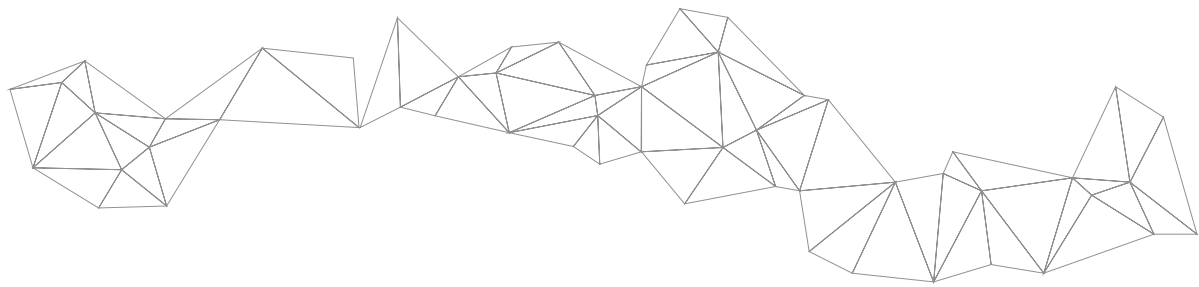
A health history for older children may include information about the number of servings of dairy products consumed by the child on a daily basis (1 cup of milk, 30–50 g of cheese,  $\frac{3}{4}$  cup of yoghurt) and questions d and e, as shown above. There are several validated short questionnaires that could be used to assess calcium and vitamin D intake in different countries.

### Biochemical testing

A specialized society (29) has proposed that children be screened for vitamin D deficiency when they:

- are breastfeeding exclusively for a prolonged duration, have dark skin and live at higher latitudes in the winter and spring months;
- present with poor growth, gross motor delays and unusual irritability;
- are taking anticonvulsants or chronic glucocorticoids or have malabsorption disorders (i.e. cystic fibrosis or inflammatory bowel disease);
- present with symptoms of vitamin D deficiency, such as unexplained bone pain, difficulty climbing stairs, waddling gait, difficulty rising from a chair or delayed walking, tetany or seizures due to low serum calcium, among others (250);
- have symptoms of rickets, such as progressive bowing of the legs and knock knees, wrist swelling, rachitic rosary, craniotabes, or delayed tooth eruption, among others (250).

Measurement of serum alkaline phosphatase has also been proposed by some authors, as a possible screening test to detect nutritional rickets in communities, as it is relatively simple, low cost and stable in the field (30). Although the [Global consensus recommendations on prevention and management of nutritional rickets](#) concluded that it could be used in the diagnosis and management of nutritional rickets, it is not recommended as a population screening test (4).



Most recently, some authors considered the potential use of alkaline phosphatase in a public health context, but found limited published evidence to support its use at the population level, as it has not yet been implemented at the country level for surveillance of nutritional rickets (104).

## **Prevention of nutritional rickets**

### **Food fortification**

#### *Vitamin D*

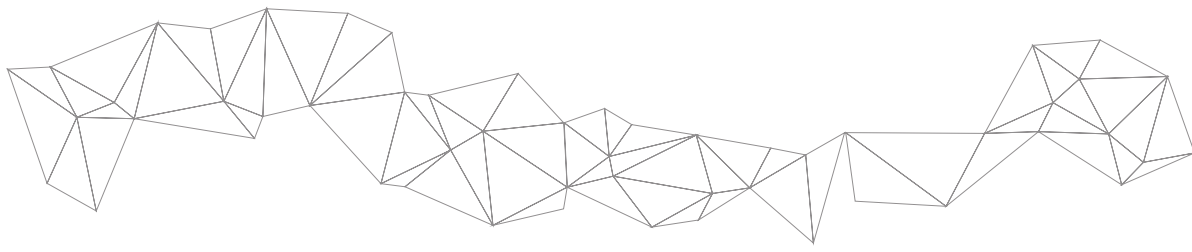
Since only a few foods are naturally rich in vitamin D, many countries have implemented vitamin D fortification programmes to help their populations consume adequate amounts of this nutrient.

Programmes for fortification of food with vitamin D started in the 1930s in Canada and the USA (20, 21). The first foods to be fortified were milk and other products. In Canada, fortification of milk with vitamin D was very successful in eradicating rickets (251, 252). Some of the additional foods that have been fortified with vitamin D include yoghurt, breads, ready-to-eat cereals, juice, oils, margarine and infant formula milks. In particular, infant formula milks are fortified with vitamin D at different levels that may vary from country to country. Four studies evaluating the vitamin D content in different fortified milks have found higher amounts of vitamin D in infant formula milks (253–256), which could be explained by the fact that some manufacturers may be adding additional vitamin D to compensate for losses that occur during processing and product shelf-life. Similar findings have been found in studies evaluating the amount of vitamin D in processed milk in the USA (254).

Fortification of staple foods with vitamin D could help maintain serum 25(OH)D at adequate levels for preventing nutritional rickets. This has been shown in some randomized clinical trials. One of these trials tested milk fortified with vitamin D (16 IU [0.40 µg]/100 mL) and bread (240 IU [6 µg]/100 g) in 201 families in Denmark with children and adults, compared to unfortified milk and bread, for 6 months (257). Another trial tested milk fortified with vitamin D (600 IU or 1000 IU in 200 mL) in 713 children in India aged 10–14 years, compared to unfortified milk, for 12 weeks (258). Fortification of atta flour (i.e. whole-wheat flour) used for preparing chapatti (an unleavened flatbread) with vitamin D (6000 IU/kg) in 64 Asian families living in England was also tested in a clinical trial (259). Finally, in Finland, fortification of milk (0.5 µg/100 g) and margarine (10 µg/100 g) was tested in a cohort of children aged 4 years before ( $n = 82$ ), and in another cohort after ( $n = 36$ ), the implementation of fortification during winter (260). All four studies showed that those consuming the foods fortified with vitamin D had mean serum 25(OH)D concentrations above 50 nmol/L (20 ng/mL) (257–260).

However, others have shown that foods fortified with vitamin D may not be sufficient to prevent vitamin D deficiency, particularly in at-risk individuals. In the USA and Canada, although vitamin D fortification is the largest contributor to vitamin D intake (65–87%), it is still not effective in reaching the estimated average requirement for vitamin D intake (261, 262). Canada has mandatory fortification of food staples with vitamin D for milk, milk alternatives and margarine. In the USA, the addition of vitamin D is required only for fortified fluid milk and fortified evaporated milk. Fluid milk in the USA is not required to have vitamin D added unless the label declares that it is fortified (261). Both countries permit voluntary fortification of certain foods. In Europe, an analysis of foods fortified with vitamin D in several countries (Denmark, Finland, Germany, Ireland, Italy, the Netherlands, Poland, Spain and the UK) showed that intake of vitamin D from fortified foods is low and has little effect on the total vitamin D intake, probably related to the fact that only a few foods are fortified and in much smaller amounts compared to North America (263).

Fortification of staple foods with vitamin D may be considered in countries with populations at risk of vitamin D deficiency and nutritional rickets. The dose of vitamin D, and the food to fortify to achieve optimal vitamin D nutrition, will vary depending on the geography and climate (countries with long winters may need higher levels), skin pigmentation, skin-coverage practices and other local and cultural considerations, as well as other current programmes for fortification of staple foods.



## Calcium

Adequate calcium intakes could be easily achieved by the incorporation of dairy products in the diet on a daily basis. However, dairy products are not part of the regular diet or are not available in certain populations. In addition, in children aged 1 year and older, calcium intakes tend to decrease as other foods are introduced in the diet, displacing milk consumption. Since chronic low calcium intake is most commonly the cause of nutritional rickets among older children, food fortification becomes particularly important for these groups. Groups at risk of low calcium intake could benefit from fortification programmes or from promotion of indigenous foods that are rich in calcium. For example, a study was conducted in Nigeria to test calcium supplementation (400 mg/day), ground baked fish (i.e. local dried catfish *Clarias gariepinus* or *Heterobranchus longifilis*; about 530 mg/day) or placebo in 647 children aged 12–18 months, with typical low calcium intakes, for 18 months. Although the study was not able to demonstrate a protective effect of the intervention on the occurrence of rickets, it found that the ground fish was readily accepted and could be a rich source of calcium in this population (95). Calcium fortification of staple foods has also been shown to be effective in improving calcium intake. A study in India tested the fortification of laddoo, a local snack, providing 400 mg/day of calcium for 12 months in 60 children aged 2–3 years, compared to a control group that received the same laddoo but without calcium, and found significantly greater gains in total bone mineral content in the fortified group and also high levels of acceptance of the fortified food (>90%) (264). Another trial tested the fortification of a ready-to-eat breakfast cereal with calcium (313 mg in two servings) compared to non-fortified cereal, in 27 children aged 6–9 years in the USA, for 2 weeks (221). Calcium intake significantly increased in those consuming the fortified cereal, and calcium absorption, as assessed using isotopes, was similar with the fortified cereal compared to milk. Other foods fortified with calcium include various flours, yoghurt, soy milk and orange juice, among others. However, there is limited evidence on the effects of consuming calcium-fortified foods to prevent nutritional rickets.

For many countries, fortification of staple foods presents several challenges at different levels (industry, government, and retail). Based on an analysis of 20 national fortification programmes in 12 countries, a critical barrier in the implementation of these programmes is related to multiple problems in regulatory monitoring of the food industry, which is crucial for ensuring that standards for fortification are met (265). Other barriers include political and financial issues. WHO has developed guidelines for food-fortification programmes, to help overcome some of these barriers (115).

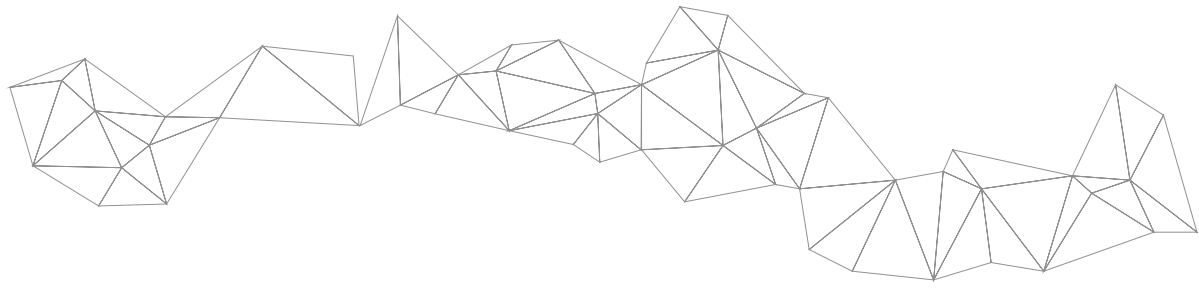
### Supplementation with vitamin D

WHO has not published guidance on the use of vitamin D supplements for healthy infants. It also does not recommend vitamin D supplementation in pregnancy to prevent the development of pre-eclampsia and its complications or for improving maternal and infant health outcomes (230).

Several committees, institutions and health organizations, such as DACH (201), EFSA (127), IOM (125), SACN (124), the Committee for Vitamin D recommendations for Central Europe (266), Health Canada (252), the American Academy of Pediatrics (7), the Canadian Paediatric Society (267), the Food Safety Authority of Ireland (268) and some expert groups (104), among others, have proposed routine vitamin D supplementation for exclusively breastfed infants, to prevent vitamin D deficiency.

For example, the American Academy of Pediatrics recommends a vitamin D supplement of 400 IU/day, to maintain serum 25(OH)D concentrations above 50 nmol/L (20 ng/mL) in breastfed infants (7). Since vitamin D deficiency can start in utero in pregnant women who are vitamin D deficient, it recommends starting supplementation soon after birth.

The Canadian Paediatric Society recommends vitamin D supplementation of 400 IU/day for all infants during their first year, increasing to 800 IU/day between October and April among those living a latitude of 55 degrees north and among those living in a latitude of 40 degrees and 50 degrees north with risk of vitamin D deficiency other than latitude alone (267). In 2007, the Food Safety Authority of Ireland



recommended that all infants, from birth to 12 months, whether breastfed or formula fed, be supplemented with 200 IU (5 µg) of vitamin D, to prevent rickets (268). The *Global consensus recommendations on prevention and management of nutritional rickets* also recommend 400 IU/day for all infants from birth to 12 months of age, independently of their mode of feeding, and 600 IU/day for all children older than 12 months (from diet and/or supplementation), to prevent rickets, based on review of the evidence (4). A few national health organizations recommend vitamin D supplementation during pregnancy, ranging from 200 IU/day to 400 IU/day (5–10 µg/day) (124, 267).

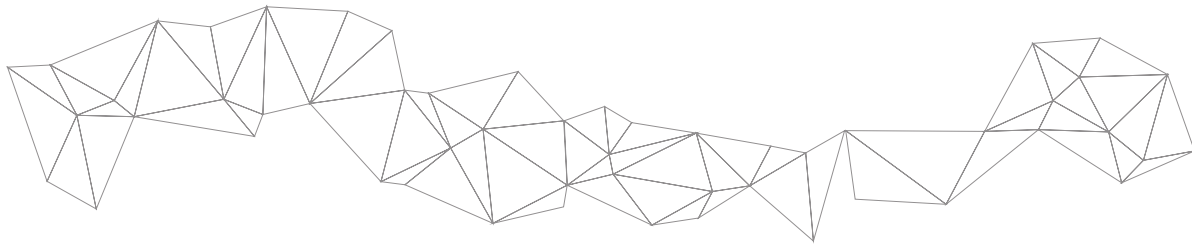
## **Treatment of nutritional rickets**

### **Supplementation with vitamin D**

Cod liver oil was first used in the 19th century to treat rickets. However, after the discovery of vitamin D, supplements have been used in different forms for the treatment of nutritional rickets (269). WHO does recognize special situations in which vitamin D supplementation may be needed. For example, it is recommended for very low-birth-weight infants at a dose ranging from 400 IU/day to 1000 IU/day (10–25 µg/day) until 6 months of age (231). In patients with tuberculosis, vitamin D (200 IU/day or 5 µg/day) is recommended as part of a multiple micronutrient supplement for improving tuberculosis treatment and nutrition (270). In undernourished HIV-infected children between the ages of 6 months and 14 years, vitamin D is recommended as part of the provision of ready-to-use therapeutic foods, in doses of 15–20 µg/100 g (271). During emergencies, WHO recommends 200 IU (5 µg/day) vitamin D as part of a multiple micronutrient supplement for pregnant women, lactating women and children aged 6–59 months (272).

Various groups have suggested different vitamin D regimens for the treatment of nutritional rickets.

- The Lawson Wilkins Pediatric Endocrine Society recommends the following (29):
  - infants younger than 1 month: 1000 IU/day;
  - infants aged 1–12 months: 1000–5000 IU/day;
  - children older than 12 months: >5000 IU/day;
  - when the condition is resolved, which usually occurs 3–4 months after treatment, a maintenance dose of 400 IU/day is suggested;
  - in settings of poor compliance maintenance dosing, it is suggested that single intermittent high doses be used.
- The *Global consensus recommendations on prevention and management of nutritional rickets* suggested the following (4):
  - infants younger than 3 months: 2000 IU/day for 12 weeks, with a maintenance dose of 400 IU until the condition is resolved;
  - infants aged 3–12 months: 2000 IU/day for 12 weeks or a single dose of 50 000 IU, with a maintenance dose of 400 IU until the condition is resolved;
  - children aged 1–12 years: 3000–6000 IU/day for 12 weeks or a single dose of 150 000 IU, with a maintenance dose of 600 IU until the condition is resolved;
  - children older than 12 years: 6000 IU/day for 12 weeks or a single dose of 300 000 IU, with a maintenance dose of 600 IU until the condition is resolved;
  - monitoring of nutritional rickets after the onset of treatment.



### **Supplementation with calcium**

Calcium supplementation has been shown to be effective in resolving nutritional rickets when the cause is dietary calcium deficit. A study conducted among Nigerian children, with various doses of calcium (500 mg/day, 1000 mg/day or 2000 mg/day) for 24 weeks, found that those in the two higher-dose groups had more rapid radiographic healing of rickets compared to those receiving the lowest dose (273). It found no differences between the two higher doses but did notice that some children required more time for complete resolution of the condition. Others have suggested doses of 30–75 mg/kg/day of elemental calcium divided into three doses (29). However, meta-analyses are needed to evaluate these suggested doses.

In children with tetany of convulsion, some experts propose treatment with intravenous calcium at a rate of 10–20 mg/kg in 5–10 minutes, repeated as needed (29).

Supplementation with calcium and phosphorus is proposed by some authors for low-birth-weight infants, to cover the need for extra calcium to support continuation of the intrauterine rate of accumulation (274).

### **Supplementation with both vitamin D and calcium**

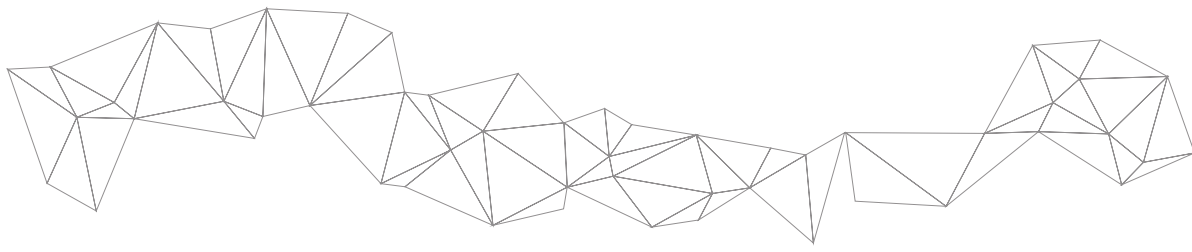
Children with nutritional rickets often have deficient intakes of both calcium and vitamin D (232, 234, 275); therefore, it has been suggested that both calcium and vitamin D supplementation be given to resolve nutritional rickets. A study in India randomized children and adolescents with rickets to calcium supplementation (1 g/day) with and without vitamin D supplementation (232). Complete healing was observed in children in both groups after 3 months; the adolescents did not respond to calcium supplementation alone, only to the combination of calcium and vitamin D after 3–9 months, indicating that vitamin D deficiency was the main problem in the adolescents. Other studies have also shown that the combination of calcium and vitamin D is more effective in resolving nutritional rickets compared to calcium alone or vitamin D alone (185, 276–279). The doses used in these studies varied considerably, with calcium doses ranging from 600 mg to 3000 mg per/day and vitamin D doses varying from 25 000 IU/month to single doses of 50 000 IU, 300 000 IU or 600 000 IU given intramuscularly and two doses of 600 000 IU given intramuscularly.

In summary, these interventions using vitamin D and calcium supplementation have been shown to be effective and rapid, with complete recovery observed as early as after 3 months of supplementation. However, further analyses are needed to evaluate the optimal doses of both calcium and vitamin D.



# **Implementing or delivering solutions through policies and programmes**





**A**side from guidance on supplementation for extremely low-birth-weight infants, WHO does not have specific recommendations on nutrition interventions for the prevention or treatment of rickets. However, some countries and national societies do recommend various supplementation and fortification interventions for increasing intakes of vitamin D and/or calcium.

Prior to implementation, a public health programme should have well-defined objectives that take into account available resources, existing policies, suitable delivery platforms and suppliers of the intervention, communication channels, and potential stakeholders. Ideally, nutrition intervention programmes should be implemented as part of an integrated programme on health, which includes addressing micronutrient deficiencies.

Considering the experiences of those within a population with the intervention is also a relevant implementation consideration: ongoing assessment of the accessibility and acceptability of the intervention can inform programme design and development, in order to increase adherence and better assess the impact of the programme. This is particularly relevant in settings where the prevailing social norms and determinants may set unequal conditions and opportunities for different groups. For instance, in some settings, gender norms may create unequal opportunities for girls and boys at any age, within and outside of school; in other settings, social perceptions around ethnicity and race intervene in how certain population groups access and use an intervention.

Programmes should be carefully designed, based on locally available evidence and experience. These can include data that can inform the implementation strategies on procurement and supply-chain issues, optimal distribution channels, behaviour-change communication and specific strategies to identify and reach the most vulnerable. These are particularly important in the absence of a well-functioning health-care system that reaches this population.

In settings where the intervention may be delivered in coordination with the education sector, intersectoral action is fundamental. The education sector is an important partner in the implementation of any recommendations referring to school-age children. Appropriate coordination mechanisms and proper training of health workers and education staff is necessary for delivery of the intervention and also for collection of data needed for programme monitoring and surveillance, including information on factors related to health inequities.

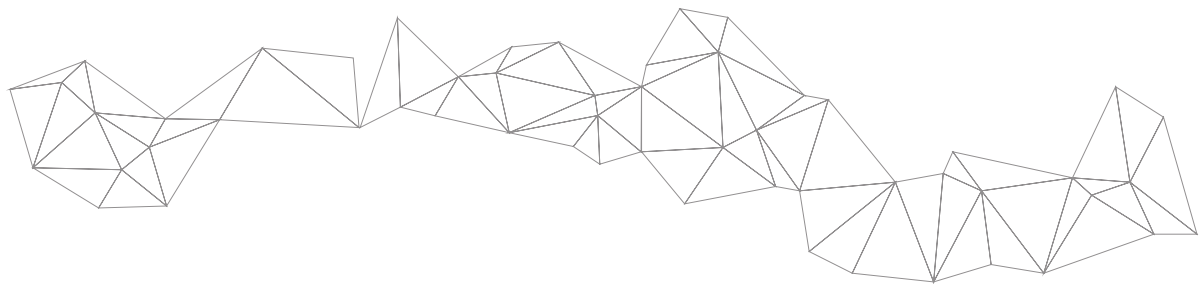
Accessing hard-to-reach population groups is extremely important during implementation stages, as it contributes to preventing or tackling health inequities and to furthering the realization of individuals' rights to health. Appropriate surveillance and monitoring systems can thus provide information on the impact of the intervention (including information on the adequacy of funding and the effectiveness of supply chains and distribution channels).

## **Regulatory considerations**

Universal access to quality, effective and safe medicines and health products is a core element of universal health coverage and therefore a priority for WHO. The need to expand access to medicines and health products is highlighted in the [Sustainable Development Goal 3](#) (280). Therefore, the access to medicines will be a key indicator for countries' progress to universal health coverage (281, 283).

Colecalciferol (vitamin D<sub>3</sub>), and ergocalciferol (vitamin D<sub>2</sub>) and calcium, are considered essential medicines, as they address a high-priority health-care need of infants, children, adolescents and pregnant women (283, 284). Essential medicines are intended to be available within the context of functioning health systems, at all times, in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford (285).





Colecalciferol is included in both the [WHO Model List of Essential Medicines for Children \(284\)](#) and the [WHO Model List of Essential Medicines \(283\)](#) as follows:

- oral liquid: 400 IU/mL;
- solid oral dosage form: 400 IU; 1000 IU.

Ergocalciferol can be used as an alternative. The [WHO Model List of Essential Medicines](#) describes the dosage forms and strengths of ergocalciferol as follows (283):

- oral liquid: 250 µg/mL (10 000 IU/mL);
- solid oral dosage form: 1.25 mg (50 000 IU).

The [WHO Model Formulary for Children](#) indicates colecalciferol for prevention and treatment of vitamin D deficiency; treatment of vitamin D deficiency caused by malabsorption or chronic liver disease; hypocalcaemia associated with hypoparathyroidism; and treatment of vitamin D-deficiency rickets. The dosage of orally administered colecalciferol is indicated for both prevention and treatment. Adequate calcium intake is necessary for a clinical response to vitamin D (286).

Calcium is included in the [WHO Model List of Essential Medicines \(283\)](#) in two different dosage forms. Calcium tablets should be available in 500 mg (elemental) dose. Calcium gluconate injections should be available in 10- mL ampoule (100 mg/ mL). The [WHO Model List of Essential Medicines for Children \(284\)](#) only includes calcium gluconate injections in 10 mL ampoules (100 mg/ mL).

The WHO Expert Committee on Specifications for Pharmaceutical Preparations has made numerous recommendations that are relevant to quality assurance and control of pharmaceutical products. WHO guidelines for medicines quality assurance regulate all the stages, from the manufacture of a pharmaceutical product such as colecalciferol, ergocalciferol and calcium through to the delivery to the population in need, thus covering production, quality control, inspection and distribution (287).

## **Ethical considerations**

Ethics refers to standards of what is right or wrong and fair or unfair, which can advise people on what to do and not do in terms of rights, obligations and benefits to society and individuals. Ethics is central to science, research, policy-making and implementation. Every field of human action, including public health nutrition, is subject to facing ethical challenges.

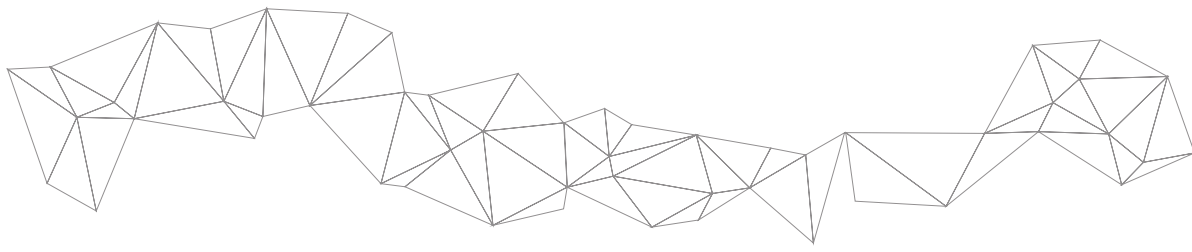
Four principles constitute the most widely accepted framework for ethics in medicine, and are used in other health-related fields: (i) respect for individual autonomy; (ii) beneficence; (iii) non-maleficence; and (iv) justice. These principles assist health workers in identifying whether an intervention is producing benefits to individuals and communities; preventing harms, at both individual and societal levels; distributing health benefits across social groups, i.e. how much an intervention is contributing to health equity; and respecting and promoting the exercise of human rights.

The delivery of micronutrient interventions to those with micronutrient deficiencies is in line with the right to health and with the aforementioned ethical principles. In addition, there are specific ethical issues that prevent the conduct of placebo-controlled randomized controlled trials on rickets in the context of previous knowledge about the prevalence. Therefore, other research methods need to be used to determine the efficacy of certain interventions for the prevention and treatment of nutritional rickets.





**Evaluating the actions for prevention or treatment of nutritional rickets**

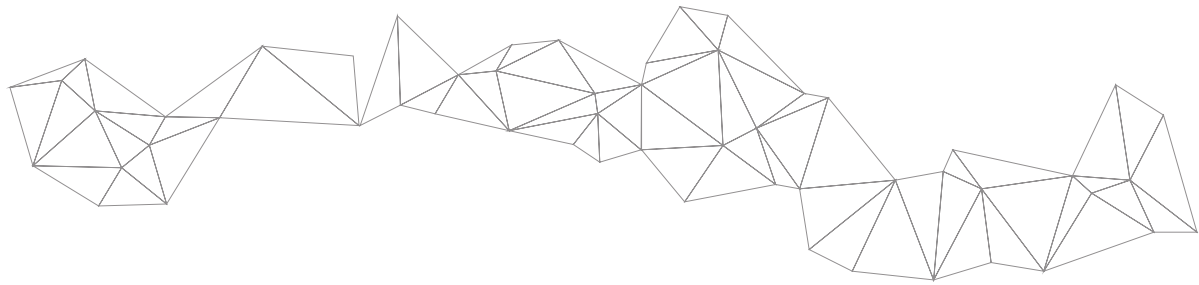


**A** plan for monitoring and evaluating micronutrient intervention programmes with appropriate indicators, including equity-oriented indicators, is encouraged at all stages (288). The WHO Department of Nutrition for Health and Development, Evidence and Programme Guidance Unit, jointly with the United States Centers for Disease Control and Prevention (CDC) International Micronutrient Malnutrition Prevention and Control (IMMPaCt) programme, and with input from international partners, has developed a generic logic model for micronutrient interventions in public health (289), to depict the plausible relationships between inputs and expected Sustainable Development Goals, by applying the micronutrient programme evaluation theory. Member States can adjust the model and use it in combination with appropriate indicators, for designing, implementing, monitoring and evaluating the successful escalation of nutrition actions in public health programmes. Additionally, the WHO/CDC [eCatalogue of indicators for micronutrient programmes](#) (290), which utilizes the logic model, has been developed as a user-friendly and non-comprehensive web resource for those actively engaged in providing technical assistance in monitoring, evaluation and surveillance of public health programmes implementing micronutrient interventions. Indicators for fortification programmes are already available, while those for supplementation programmes are currently being developed. A list of potential indicators with standard definitions can be selected, downloaded and adapted to a local programme context. The eCatalogue will serve as a repository of indicators to monitor and evaluate micronutrient interventions (290). While it does not provide guidance for designing or implementing a monitoring or evaluation system in public health, some key indicators may include useful references for that purpose.

Since 1991, WHO has hosted the Micronutrients database with the [Vitamin and Mineral Nutrition Information System](#) (VMNIS) (291). Part of WHO's mandate is to assess the micronutrient status of populations; monitor and evaluate the impact of strategies for the prevention and control of micronutrient malnutrition; and track related trends over time. The Evidence and Programme Guidance Unit of the Department of Nutrition for Health and Development manages the VMNIS micronutrient database, through a network of regional and country offices, and in close collaboration with national health authorities.

For evaluation at the global level, the WHO Department of Nutrition for Health and Development has developed a centralized platform for sharing information on nutrition actions in public health practice implemented around the world. By sharing programmatic details, specific country adaptations and lessons learnt, this platform will provide examples of how guidelines are being translated into actions. The [Global database on the Implementation of Nutrition Action](#) (GINA) (292) provides valuable information on the implementation of numerous nutrition policies and interventions. The use of GINA has grown steadily since its launch in November 2012.

An efficient system for the routine collection of relevant data, including relevant determinants of health, therapeutic adherence, and measures of programme performance, is critical to ensure intervention programmes are effective and sustained, and drivers to the achievement of the right to health for all population groups. Monitoring differences across groups in terms of accessibility, availability, acceptability and quality of the interventions contributes to the design of better public health programmes. The creation of indicators for monitoring can be informed by the approaches of social determinants of health (293), so inequities can be identified and tackled. It is particularly important to design sound implementation strategies to serve as the base for scaling up efforts. Appropriate monitoring requires suitable data, so efforts to collect and organize information on the implementation are also fundamental.



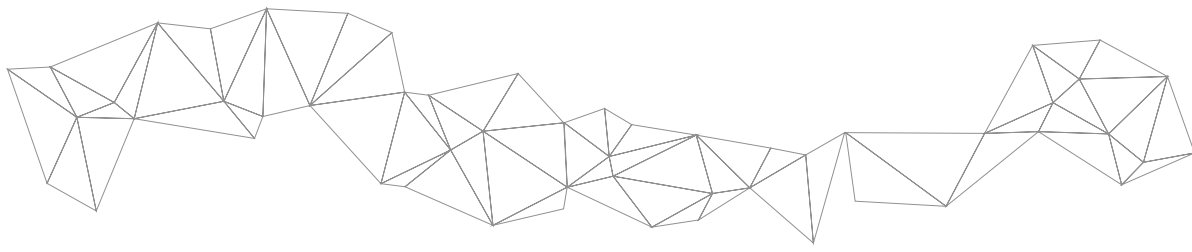
## Knowledge gaps

**A** critical research gap in nutritional rickets is determination of how to effectively prevent rickets, from a public health or primary prevention perspective. In particular, more research is needed on the detection of mild rickets with effective screening tools and programmes, and on the effectiveness of potentially implementing a global recommendation for using vitamin D supplementation in infants and how to implement supplementation in places where it is not currently part of the standard of care, such as in many low- and middle-income countries.

Dose–response studies testing different vitamin D doses, dose frequencies and administration routes are needed in infants and children, for the treatment of vitamin D deficiency and for vitamin D maintenance; during pregnancy and lactation for the prevention of vitamin D deficiency in infants and of neonatal rickets and hypocalcaemia; and for assessment of vitamin D status throughout the first year of life.

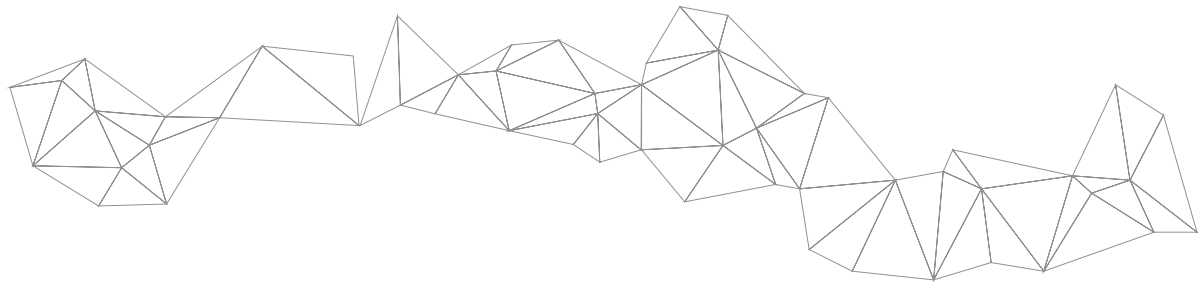
Further analysis is needed to determine the best combination of diagnostic tools to most accurately diagnose rickets. Currently, clinical signs based on physical examination, biochemical tests and radiographs are used, but without consensus regarding how to interpret and combine these. An update is needed for establishing thresholds for serum levels of vitamin D associated with rickets. The meta-analysis conducted in 2007, including 13 studies (one randomized controlled trial, four before-after studies, eight case-control studies), showed fair evidence of an association between lower serum 25(OH)D levels and rickets (46). Many new trials have been published since 2007 assessing the association between different concentrations of vitamin D biomarkers and rickets (12, 40, 41, 49, 51, 71, 77).

There is also a need to establish the optimal dose and duration of vitamin D and calcium supplementation to prevent and treat rickets. In 2007, a systematic review was conducted on interventions for the prevention of nutritional rickets in children (3). However, only four trials with about 1700 participants and with a duration of 9 months to 2 years were included, with no clear indication of the dose to be given. They did report that the combination of vitamin D and calcium supplements was effective. Currently, there is a protocol under way for a systematic review to evaluate vitamin D supplementation for the prevention of vitamin D deficiency in preterm and low-birth-weight infants (294).



## Final considerations

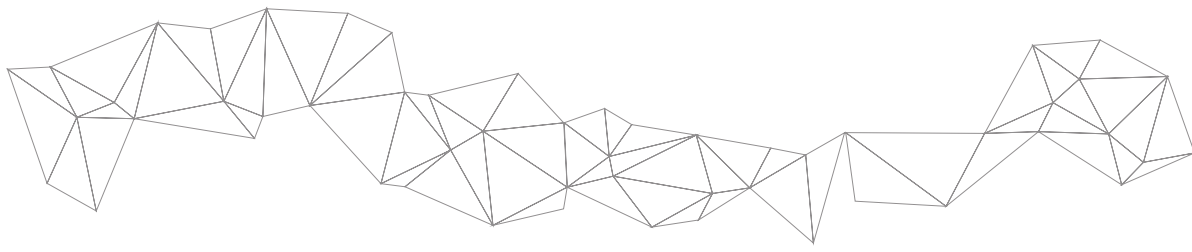
**R**ickets is a skeletal disorder that occurs in growing children, owing to failure of mineralization of the growth plate and osteoid matrix (1–4). It has devastating consequences but these are often poorly recognized. It is associated mainly with growth problems, bone pain, muscle weakness, limb and pelvic deformities, failure to thrive, developmental delay (such as gross motor delays in sitting, crawling and walking) and dental anomalies (8–12). Its peak incidence occurs among infants and young children aged 6–23 months and in adolescents aged 12–15 years, though it may also occur in children aged between 2 years and 11 years (6–9). Case-reports of rickets first appeared in the late 18th century (18) and became endemic by the 20th century (19), after which fortification of foods with vitamin D started and virtually eradicated the condition. Most recently, various reports have suggested a resurgence of the condition, with a reported prevalence of rickets as high as 72% in Mongolia (87). Rickets is mainly caused by deficient intakes of vitamin D and/or calcium, or physiological problems associated with the metabolism of these nutrients. Low calcium intake has been reported as common worldwide; however, there are only a few countries with data reported at the national level. Vitamin D deficiency is also highly prevalent worldwide in infants (particularly those who are exclusively breastfed), children, adolescents and pregnant women (particularly among girls and women from the Middle East), mainly related to low vitamin D intake or lack of sun exposure. There is no clear diagnostic definition for nutritional rickets, which is needed to be able to quantify the magnitude of the problem worldwide, compare prevalence rates between populations and develop appropriate guidelines for its prevention and treatment. In general, nutritional rickets has been diagnosed based on the combination of several parameters, including health history (such as breastfeeding, history of calcium intake, use of supplements) and clinical signs based on physical examination, biochemical testing and radiographs. Radiographs have traditionally been considered to be the reference standard in diagnosing rickets. However, further analyses are needed to evaluate the specificity and sensitivity of all these indicators. Among healthy individuals, the WHO/FAO-recommended nutrient intake of vitamin D is 200 IU/day (5 µg/day) for infants, children and adolescents and for calcium this varies from 300–400 mg/day in infants to 1300 mg/day in adolescents (128). For prevention of nutritional rickets, the use of food fortification or direct supplementation may be needed. However, there is no consensus regarding the levels to be used. For treating nutritional rickets, interventions using vitamin D and calcium supplementation have been shown to be effective and rapid, with complete recovery. More studies are needed to determine effective public health interventions for preventing and treating rickets and for evaluating effective screening tools and intervention programmes in pregnancy and early in life.



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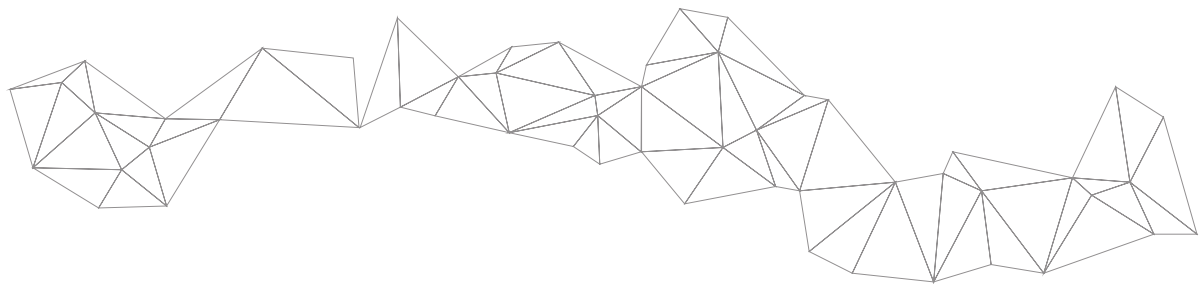
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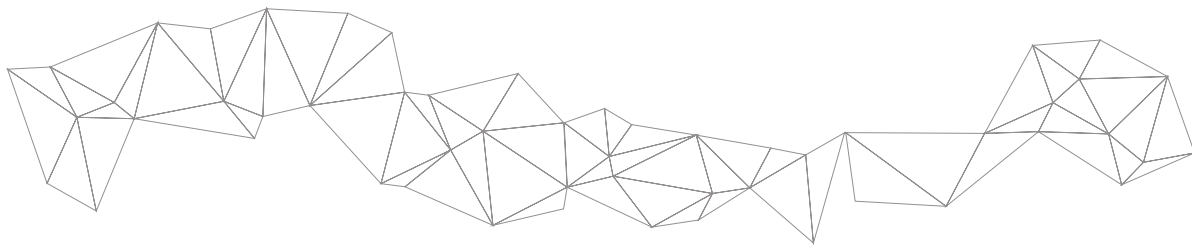


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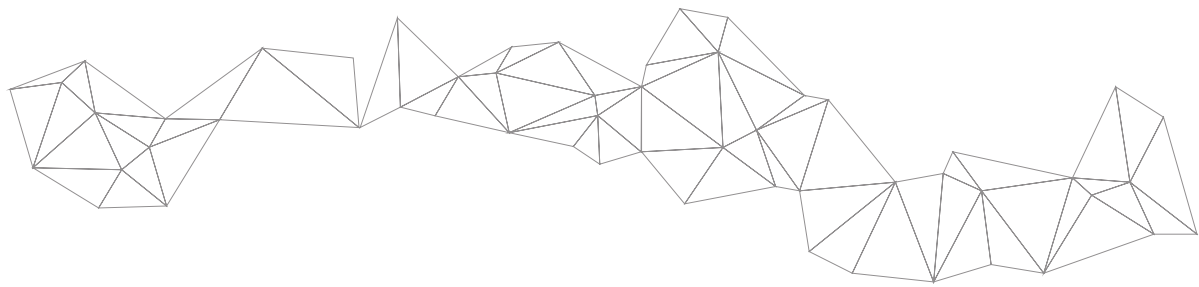




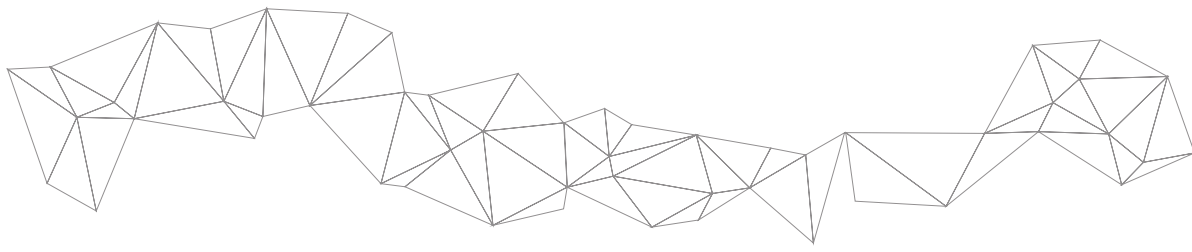
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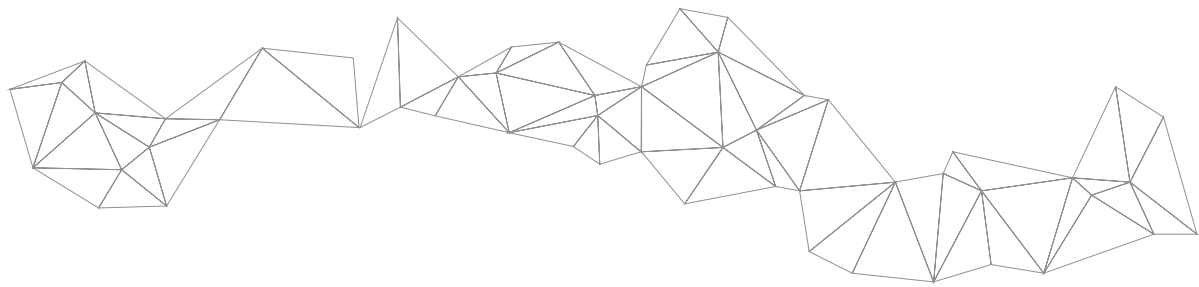
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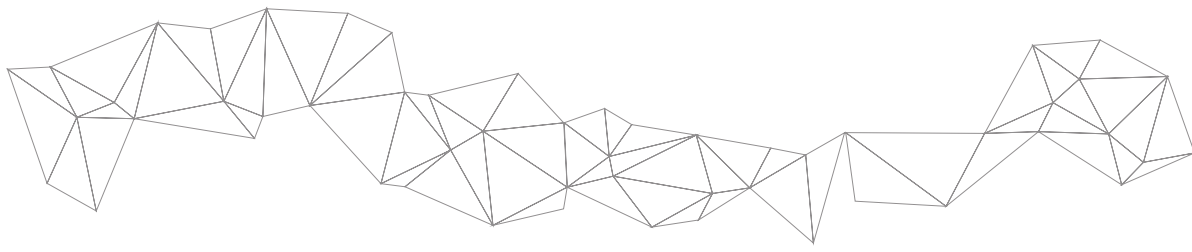


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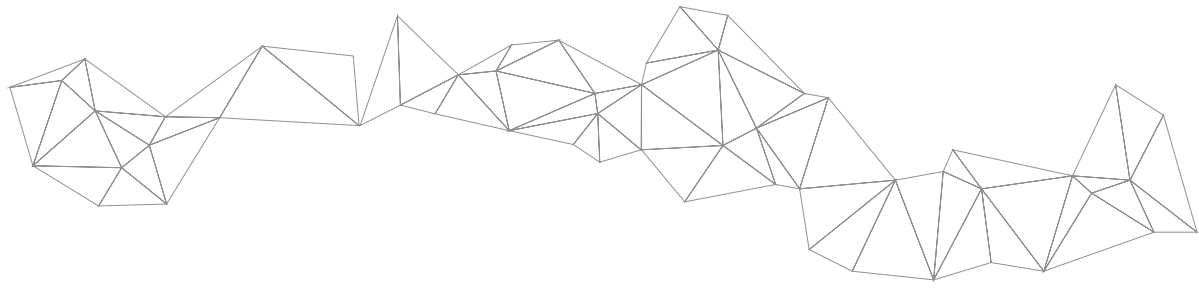


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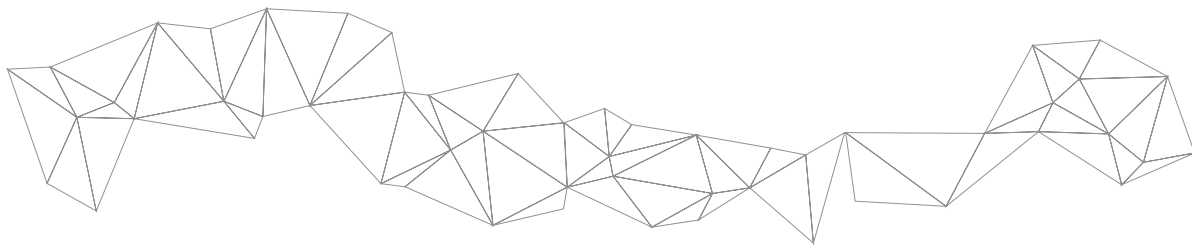




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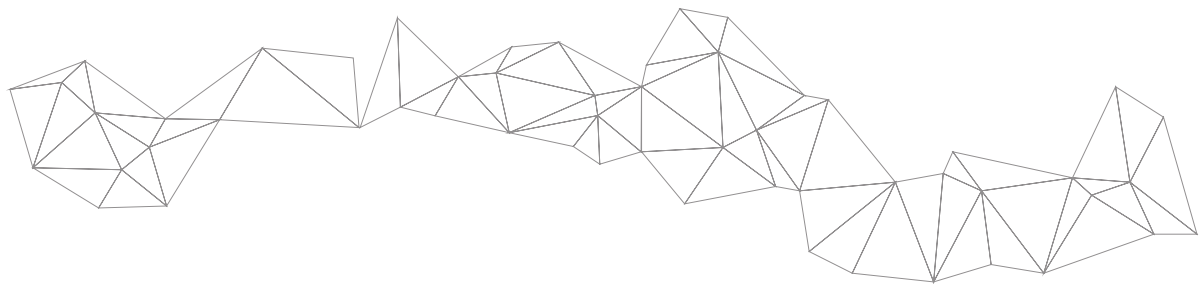


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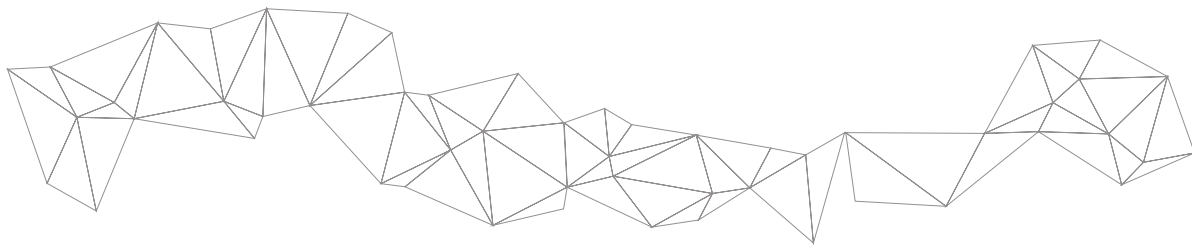


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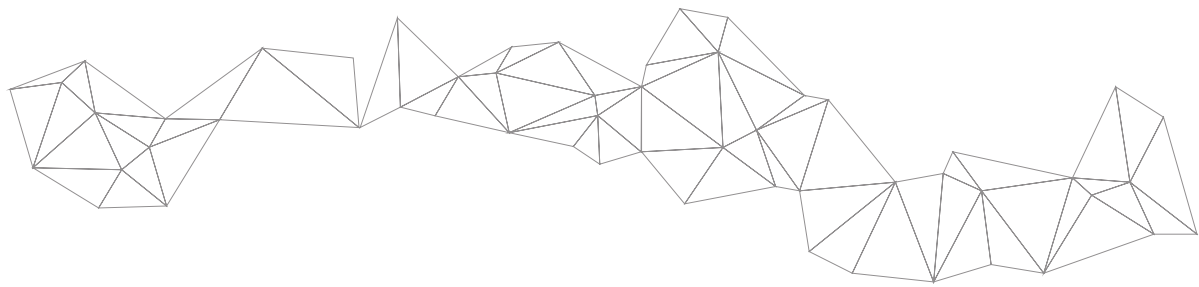




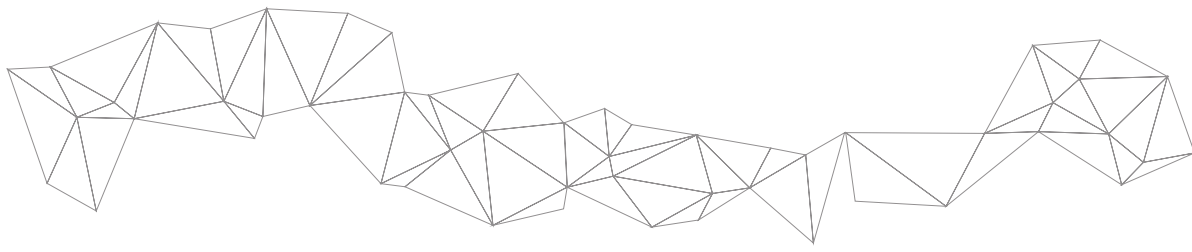
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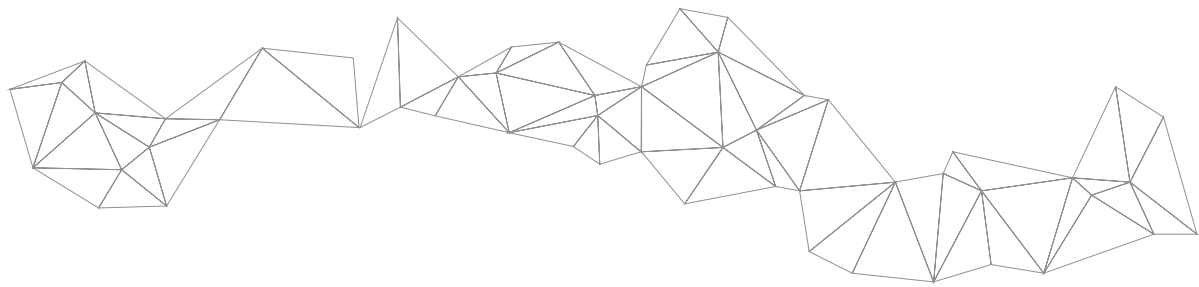
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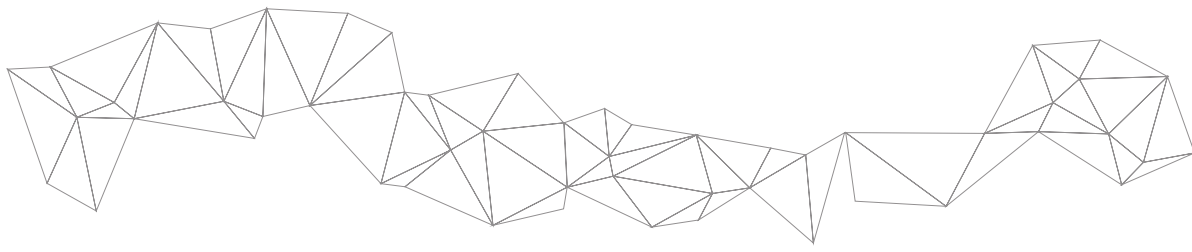


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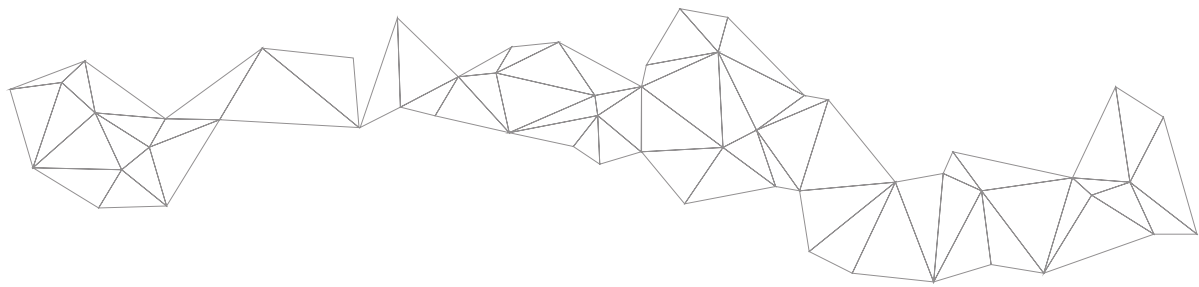


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