Nutritional rickets: Historic overview and plan for worldwide eradication

Roger Bouillon, MD, PhD, FRCP (London) and Leen Antonio MD, PhD.

Laboratory of Clinical and Experimental Endocrinology, Department of Chronic Diseases, Metabolism and Ageing, KU Leuven, Belgium. RB: ORCID: 0002-6446-3763; LA: ORCID 0000-0002-1079-2860

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Abstract:

Rickets was first described in great detail in the mid 17th century and was affecting a great number of children in major European cities. The disease, however, existed already in the Roman times. The etiology of this disease remained enigmatic until the 1920s when two different mechanisms, lack of exposure to sunlight and lack of a dietary factor were finally solved by the discovery of vitamin D and its dual origin. Soon thereafter, the implementation of vitamin D supplementation for all infants and small children largely eliminated nutritional rickets in Europe and North America. It took nearly a century to elucidate the complex chemistry, metabolism, mode and spectrum of activity of the vitamin D endocrine system. Nutritional rickets, whether due to simple vitamin D or calcium deficiency or both, remains widely ravaging many infants and children around the world. Asian countries and the Middle East are mainly confronted with vitamin D deficiency whereas many African and some Asian countries face calcium deficiency rickets. Immigrants and refugees or in general people with a darker skin living in moderate climate zone are also confronted with this disease. There is great consensus how this disease could be prevented or cured. In collaboration with most international professional societies, we prepare a memorandum, in line with the successful battle against iodine deficiency disorders, to convince the World Health Organization and its member states to start an implementation program to eradicate nutritional rickets by 2030.

Nutritional rickets in humans before the discovery of its etiology.

Rickets was first clearly described in the medical literature in the mid-17th century by Whistler at the Leiden University in The Low Countries (1645) and a few years later by Glisson (1650) in London [1–3].

The Dutch physician, Arnold Boot (Arnoldi Booti in his Latin publication of 1649) stressed that it was mainly a disease of young children (<3 yrs), with as major consequences thoracic malformations (“chicken breast” or “pectoream tabem” in Latin) and swelling of joints (called “doubling” of the joints). He hypothesized the cause should be sought in the enlargement of the liver due to excess or poor nutrition of the mother or foster mother [3]. Many other authors also described the clinical picture and discussed its origin and treatment (for review see: [4–10]).

The disease was highly frequent in many areas of the Western world and especially in big cities. Rickets was also frequently mentioned as the cause of death in the London city cemetery death records from the 17th century onwards [5]. The disease, however, was already present much earlier in human history. Out of about 400 mummies from ancient Egypt, examined with CT scans, only one case of rickets was found in a child with massive hydrocephalus (José Luis Neyro Bilbao, personal communication, 2018), indicating that rickets must have been very rare along the Nile valley. In an overview of radiographic examinations of skeletons from 18 cemeteries from 15 settlements in the Mediterranean and North-West Europe dating to the first centuries [11,12], 2787 skeletons were evaluated for signs of rickets. Overall, about 5.6 % of skeletons from subadults (<18 yrs) and 3.2% of all adult skeletons showed signs of active or cured rickets or osteomalacia; the highest (7%) frequency was found in skeletons of subadults in Ostia, the port city of ancient Rome, a city with high rise (> 6 stores) buildings. This should not be a surprise as the famous Roman physician, Soranus Ephesius (98-138 AD) already gave a good description of the disease with muscle weakness and soft bone, resulting in bowed legs. He also mentioned that this disease happened more in the neighborhood of Rome than in other places of the Roman empire (cited in [13]). Findlay also mentioned that the disease has never been mentioned in Egyptian medical papyri. Several skeletons from the de Medici family also showed

signs of rickets [14], but it is of course unclear whether this would be of a genetic or nutritional origin. In 19th century England, in a small town north of London, 138 out of 642 skeletons showed signs of rickets (21%) in subadults [15,16]. In the Beemster population, a 19th century rural community in the Netherlands, 30% of children between the ages of two and four years ($n = 7/23$) had rickets, whereas residual signs of rickets were found in 14% of 200 adults (20% in women) [17]. There is increasing attention to the presence of rickets from medieval times until the discovery of the cure of rickets. In an overview of Watts et al., signs of rickets were present in 3.9 to 35 % of skeletons from the 11th to the 19th century found in Northern Europe or North America [18].

In the beginning of the 20th century, nutritional rickets was extremely frequent in many areas around the world as documented in post-mortem analysis of children who died for whatever reason in Dresden, Vienna or Baltimore. In one of these studies, Schmorl [19] reported that mild or severe rickets was found in 94% and 45%, respectively, at autopsy of young children during the 1901-1908 period in Dresden (Germany). Similarly, Follis et al. reported that, based on autopsy data, 56% and 72% of all white or black children, respectively, aged 0-2 years of life, have some form of rickets and 8% and 33% had severe rickets (Baltimore area, 1926-1942) [20]. Hess et al. put it more bluntly in a JAMA paper: “all “negro” children living in New York have some degree of rickets” [21]. In Belgium, at the beginning of the 20th century, about 21% of conscripts for the army were disqualified for active service based on skeletal malformations (“chicken breast”) due to the consequences of childhood rickets. Therefore, before the discovery of the cause of rickets, the disease had epidemic proportions in several major European cities but was also present in many children from North America. Glisson in the mid-17th century mentioned that the disease was more frequent in children of rich families and with hindsight, this can be explained as the parents avoided that their children would be exposed to sunlight and their diet was a combination of meat and bread and therefore had a low calcium but high phosphate content. The disease was also present in children of wealthy Indian families (who also avoided sun exposure of their children as to keep them “as white” as possible). Later on in history, rickets became

a disease of poor children living in poor conditions. Indeed, the disease was very frequent in the poorest families who lived in slums of big cities with heavy air pollution due to burning of coal or peat.

Did rickets affect vertebrates earlier in their ~ 600 Million years of evolution?

Whether rickets already occurred early during the evolution of vertebrates is not well documented. Raising rainbow trout during a very long time on a vitamin D deficient diet and without exposure to UVB light resulted did not cause a bone phenotype [22]. Deletion of CYP2R1 in zebrafish resulted in visceral obesity but did not cause rickets [23], whereas in humans such null mutations cause rickets [24]. However, frogs and chicks develop severe rickets when fed a vitamin D deficient diet without exposure to sunlight [25,26]. Similarly, many animals kept in zoos without special dietary or lifestyle precautions frequently developed rickets. Indeed, when more than 20 successive litters of lion cubs at the London Zoo died, John Bland-Sutton, a prominent London physician, advised (in 1889) to switch their diet of lean horse meat into a combination of goat meat and bone supplemented with cod liver oil [27]. Subsequent litters were raised successfully. This empirical diet contained exactly what is needed: a good calcium intake, a good calcium:phosphate ratio, and a supplement of vitamin D and taurine (as lions are unable to synthesize vitamin D from 7-dehydrocholesterol nor are they able to synthesize taurine, which is essential for bile acid conjugation and intestinal fat absorption). To what extent this clever recommendation influenced later use of diets to discover the true origin of rickets is unclear. Pet animals (especially lizard or reptiles in general, kept by children as dinosaur-like creatures) are also prone to rickets due to a combination of lack of UVB exposure and inadequately high phosphate/calcium ratio in their diet [28]. Domestic animals are also known to develop rickets when they do not receive a diet with the appropriate calcium:phosphate content or lack dietary vitamin D or sun exposure [29]. Monkeys are also prone to rickets when kept in zoos [30]. A special situation is that of New-World monkeys who normally live in treetops of the Amazonian forest. They developed rickets in the San Diego zoo even when exposed to plenty of sunlight. These animals evaded “natural”

vitamin D toxicity in their natural habitat by producing a chaperone protein that decreases binding of (several) nuclear receptors (including VDR) to their DNA responsive elements [31] and thereby become relatively vitamin D resistant. Also koalas in zoos need vitamin D supplements to avoid rickets [32].

From these data, it seems that most vertebrates can develop rickets when they lack access to sunlight or when fed an unnatural diet. Therefore, it seems that, as in humans, nutritional rickets is mainly a man-made disease, due to lack of sufficient exposure to sunlight and deficient vitamin D intake.

Discovery of the etiology of nutritional rickets.

From the early detailed description of rickets in the mid-17th century until the discovery of the dual origin of vitamin D and the clear solution to cure and to prevent rickets, many hypotheses have been postulated (Table 1). Some initial ideas were rather phantasy but at several occasions, the cure of rickets was nearly within hands. This was reviewed in great detail in “300 jaren rachitis onderzoek” (in Dutch; this monograph of 300 years of rickets (1645-1945) has unfortunately never been translated in English) by Marius Tausk, the medical director of Organon [8]. However, Olav Byvoet used some of the data in that publication in an extensive review [4].

The discovery of the origin of nutritional rickets has been reviewed many times [4–6,33] and will therefore not be extensively reviewed here. In essence, Edward Mellanby in the UK found that rickets in dogs could be prevented by feeding them a high fat diet or cod liver oil. Initially, it was thought that vitamin A might be implicated. McCollum in the US however, demonstrated that the “vitamin” in cod liver oil was not vitamin A as it resisted oxidative heating. The new vitamin therefore received the name vitamin D, as vitamin A, B and C were already known by the early 1920s (Table 2). The discovery of the curative or preventive characteristics of cod liver oil was not totally new as liver oil from cod fish or crows was already known to be able to prevent rickets for more than one century (reviewed in [4,6,8]).

In the classical nutritional study of Hess, black children living in a poor quarter of New York who all had some signs of rickets at baseline, were treated with **cod liver oil** [21]. After 6 months nearly all children who regularly took cod liver oil, were cured of rickets whereas the ones that were only treated for 4 months showed inconsistent improvements. The ones that did not take the cod liver oil showed worsening of the disease. Hess, a well-known physician, thus became the first to show the benefits of cod liver oil in a pseudo randomized controlled study. Moreover, ***Hess succeeded in generating sufficient political support to implement a prevention program (to start in winter months) for black and Italian children in New York.***

A major well-planned clinical trial was organized in post-war Vienna by Chick (working intermittently in Vienna on behalf of the UK Medical Research Council and the Lister Institute of preventive medicine). From January 1921 until May 1922, with a nearly laboratory experiment accuracy, 75 very young children (mostly illegitimate babies, aged 1 week to 5 months) without radiologic signs of rickets at baseline, were randomized to receive different diets with or without cod liver oil. The experiment took place in two university hospitals in Vienna. No rickets was observed during the subsequent summer months, but 14 out of 21 children on the regular diet without cod liver oil developed rickets. In a subsequent curative trial, cod liver oil could cure radiological and clinical signs of rickets within 4 weeks. Similarly, exposure to ultraviolet irradiation (mercury vapor quartz lamp) or exposure to daylight/sunlight was also able to cure rickets but the most rapid improvement was found in children receiving the combination of cod liver oil and sunlight. This work was summarized at the occasion of a 1974 Prize Lecture of the British Nutrition Foundation, given by Dame Harriette Chick herself (shortly before her 100th birthday!). What has frequently been overlooked is Chick's description of "hunger osteomalacia" in post-war Vienna, with a clear clinical presentation of severe osteomalacia in poor undernourished elderly subjects. Use of cod liver oil, butter and dried eggs could clearly heal this disease in 39 inpatients as well as in 177 outpatients, allowing them to walk again within 3 weeks. Subjects who received olive oil or margarine did hardly improve [34].

The clinical value of exposure to **sunlight or UVB irradiation** to prevent or cure rickets has a complicated history (Table 2). Well before the 1920s, several experts had already linked lack of exposure to sunlight with rickets, based on seasonal variation in rickets, different incidence between children growing up in crowded cities or in rural circumstances or geographical differences. The French physician Trousseau (from the Trousseau sign of hypocalcemia) clearly blamed rickets and osteomalacia (claimed to be the same disease at different age!) to a faulty diet with a sunless climate [35]. Palm also concluded that rickets incidence was inversely related to exposure to sunlight [36]. Hutchison (UK) already mentioned that rickets was more frequent in children of rich families in British India (Hindus and Muslims) “due to lack of fresh air, sunlight and exercise”, and therefore was one of several physicians linking sun exposure to rickets [37]. Huldshinsky, however, clearly showed in 1919 that rickets can be cured by artificial UV light (mercury vapor lamp) [38] and Chick et al. independently also found that rickets in children could be prevented or cured by exposing them to sunlight or to artificially induced ultraviolet light [39] (see [34] for reprint). Hess et al confirmed these findings [40] (reprinted in [41]), [42–44]. Indeed, irradiation of one arm could cure rickets in both arms, so UV light must generate a circulating factor able to cure rickets.

The two observations – the dietary origin of vitamin D and the ability of UVB to produce vitamin D - were then “fused” into one compound by demonstrating that rickets could be cured by prior UVB irradiation of food items that were naturally not able to cure rickets (Table 2). Similarly, Steenbock [45] and Weinstock [46] showed that irradiation of yeast was able to produce a “vitamin D”, later identified as vitamin D₂. Two grams of vitamin D₃ was isolated from 150 kg of tuna liver oil by Brockmann in 1936 [47]. The chemical synthesis of vitamin D by Adolf Otto Reinhold Windaus, a German chemist, was awarded by a Nobel prize in 1928 [48,49].

The discovery of the dual origin of vitamin D provided methods to prevent or cure endemic or nutritional rickets. An implementation policy was rapidly introduced in many countries using one teaspoon of cod liver oil, oral vitamin D supplements or vitamin D-enriched food. Therefore, nutritional rickets was largely eliminated as a major disease of children in most Western countries. Different

countries used different strategies but overall the results were impressive. Both vitamin D₂ and D₃ were used (D₂ mainly in the US and D₃ mainly in Europe). The dose needed to prevent the disease was based on clinical experience and not based on randomized trials. In fact, very few RCTs have even been published apart from one in Turkey and one in China [50,51].

Diagnosis, prevention and treatment of nutritional rickets in the 21th century.

a. Diagnosis of rickets

Historically, rickets was diagnosed on the basis of clinical symptoms, with craniotables and cranial bossing, and widening of the costochondral end of the ribs (rachitic rosary) and wrists are the first symptoms. Muscle weakness (“sloppiness”) and tetany are more general symptoms. Exceptionally, severe rickets may affect cardiac function with potentially lethal cardiomyopathy [52]. Inversely, autopsy of children with unexplained sudden death frequently showed severe vitamin D deficient bone disease [53,54]. Bowing of the arms or legs occur later on when the child is able to crawl or walk. More permanent consequences are hypomineralization of teeth (enamel and dentine) and permanent deformities of legs, thoracic cage (chicken or pigeon breast and Harrison groove) or pelvis (with potential major consequences for women during delivery of their children). Later studies included histology (increased unmineralized osteoid and less mineralized bone and especially very long mineralizing lag time). Radiology allows a more objective and early diagnosis and scoring of the severity of the disease.

There is great consensus about the criteria that should be used for the diagnosis of rickets in field circumstances or in a clinical or research setting [53,55–60]. Although clinical signs of rickets are extremely useful when performed by well-trained (para)medical experts, confirmation by radiology is essential for confirmation of the diagnosis as this technique usually substantially reduces the real incidence of rickets [61].

Nutritional rickets of course should be distinguished from other causes of rickets (reviewed in [62]). A detailed description of the diagnostic criteria has been published in several consensus or review document [63]. Serum concentrations of 25OHD may help to define the etiology of rickets as most infants or children with clinical rickets will have concentrations below 12 ng/ml, with a somewhat higher threshold in case of severe calcium deficiency [64].

b. Diagnosis of vitamin D or calcium deficiency

A very different approach to estimate the prevalence or risk of rickets is the measurement of serum 25OHD in the population to estimate the risk of **vitamin D deficiency rickets**. Indeed, there is a reasonable consensus that serum 25OHD concentrations below 30 nmol/l or 12 ng/ml increases the risk of rickets (or osteomalacia) (reviewed in [55,56,65]).

This threshold needs a critical re-evaluation using more accurate mass spectrometric methodology [66]. Moreover, the threshold may be different according to the prevailing calcium intake, as African children with a low calcium intake develop rickets with somewhat higher serum 25OHD than calcium replete children [67].

Calcium deficiency can cause rickets in some but not all animals as observed about a century ago when searching for the etiology of rickets. Walker still clearly doubted whether low intake of calcium might cause rickets [68]. In humans, it took a long time before a poor dietary intake of calcium was linked to clinical rickets [69]. Another early example is that of a 1 year-old girl who received an extremely low calcium diet (less than 100 mg/d) for 8 months. Her severe rickets was cured by calcium infusions [70]. Calcium deficiency as more frequent cause of nutritional rickets, and called **calcium-deficiency rickets**, has been first recognized in African countries such as South Africa and Nigeria, but afterwards in many countries with habitual low calcium intake [61,71–74].

Calcium-deficiency rickets, however, has also been described in Europe and North America, if infants are fed on a milk substitute with low calcium content [75]. Calcium-deficiency rickets usually affects somewhat older children than simple vitamin D deficiency rickets. The pathogenesis is considered to

be a sequence of low calcium intake, secondary hyperparathyroidism and low serum phosphate causing the growth plate abnormalities typical for rickets. However, such children also have high serum $1,25(\text{OH})_2\text{D}$ concentrations and very high $1,25(\text{OH})_2\text{D}$ can regulate a number of genes in bone cells creating excess pyrophosphate (PPi) and osteopontin. This then causes a direct inhibition of mineral deposition and osteomalacia [76].

Calcium-deficiency rickets is characterized not only by high serum $1,25(\text{OH})_2\text{D}$ concentrations but also by a high percentual active intestinal absorption while absolute absorption is low, whereas the opposite is true for vitamin D deficiency (or resistant) rickets [77,78].

Measuring calcium absorption is not a practically useful diagnostic technique. Serum FGF23 concentrations are also frequently increased in calcium deficient children in The Gambia, but again this could be linked to the high serum $1,25(\text{OH})_2\text{D}$ concentrations and certainly can enhance renal calcium loss [79]. It is therefore not unlikely that hypophosphatemia (driven by high PTH and FGF23) is mainly responsible for the growth plate abnormalities; and high $1,25(\text{OH})_2\text{D}$ contributes to the bone phenotype (osteomalacia) of these children [80].

A low calcium intake can of course be caused or aggravated by gastrointestinal problems or by high intake of phytates or oxalates, capable of decreasing the solubility and intestinal absorption of calcium [71]. This combination of low calcium and high phytate intake is probably the main reason for such type of nutritional rickets in India. The distinction between both types of nutritional rickets is not always simple as vitamin D and calcium deficiency can of course frequently be found in various degrees in many countries [80].

Prevalence of rickets or vitamin D deficiency

a. Prevalence of nutritional rickets

Prentice et al. published an excellent overview [81] on the prevalence of rickets, whereby very large differences were found around the world, affecting more than one third of infants in some countries.

A more recent re-evaluation of clinical, radiological rickets or vitamin D status in children also revealed a very wide range of prevalence of rickets or severe vitamin D deficiency [56].

A summary of some major findings in *non-Western countries* is presented in Table 3. This confirms older data from Prentice, that rickets is highly endemic in Mongolia, Tibet and Northern China, as well as Northern India. There is increasing attention to the frequency of “hidden” rickets, as shown by many recent reports in a large number of countries. The Middle East is not spared from rickets even in the presence of intensive sunlight [82]. In a survey of 800 “healthy” children in Cairo, 1.12 % of the children below 18 months showed clear signs of rickets, probably due to a combination of vitamin D and calcium deficiency [83]. Also in sunny Saudi Arabia rickets was frequent in the Riyadh as well as in the Al Medina area, as 136 cases of rickets were observed in just 6 months in the main referral hospital serving the Al Medina region (being the equivalent of about one case a day) [84]. Similarly rickets was found in Taiwan, nearly all countries of the Middle-East and Northern Africa [85].

Although it was thought for a long time that Africa (apart from North Africa) was largely spared from severe vitamin D deficiency, more recent studies revealed that rickets is prevalent in some African countries, either due to poor vitamin D status, poor calcium intake or a combination of both. In an overview of several African and Asian countries [61], the prevalence of nutritional rickets varied between about 1 and 10 % (with even 42 % in the Chinese Shanxi province) based on clinical symptoms, and between 0.6 and 3.3 (The Gambia) and 3.7 (Shanxi province) when better medical examinations were used (dealing with African and Asian countries).

Overall, however, there is a major lack of well-planned representative studies on the incidence of rickets or severe vitamin D deficiency in (very) young children. The incidence of rickets has changed over time when strategies to improve the vitamin D status of the population in general or of specific target groups (infants) have been implemented (as is the rule in many Western countries for many decades). The most remarkable finding is that of Turkey with a spectacular fall of incidence from 6 to

0.1% from 1998 to 2008, by general awareness of the high risk of rickets in the population, and implementation of a supplementation policy [86].

Rickets is much less frequent in most **Western countries** that have adopted a strategy to implement vitamin D supplementation of all infants and small children. Nevertheless, nutritional rickets is still observed in these countries, but at a low overall incidence below 0.01% in large surveys in Canada, New Zealand and the UK (Table 4). However, in all these countries there are subgroups with a much higher incidence/prevalence of rickets because they do not follow the overall guidelines of systematic vitamin D supplementation in all infants. Indeed, the incidence of rickets is about 100 or more fold higher in specific risk groups, such as infants with moderately pigmented or dark skin, on prolonged breastfeeding without vitamin D supplementation and/or when born from modestly or severely vitamin D deficient mothers. In many Western countries this implies especially infants and children from refugees or immigrants from non-Western countries [56,87]. Indeed, up to 50% of at random selected school children from immigrants or refugees living in the Rotterdam area in the Netherlands had serum 25OHD concentrations below 25 nmol/l (10 ng/ml) [87]. These children usually have a more pigmented skin. Non-western immigrants and refugees often wear skin-covering clothes due to religious or cultural tradition. The food contains little vitamin D with the exception of fatty fish. In addition, many immigrants have a low calcium intake. Similarly, in the opposite part of the world, Robinson et al. described 126 cases of X-ray confirmed rickets in Sydney, Australia, with a doubling of the number of cases over time [88]. The disease was nearly exclusively observed in recently immigrated children or first generation offspring of immigrant parents, with the region of origin predominantly the Indian subcontinent (37%), Africa (33%), and the Middle East (11%). In addition to the general survey on rickets in Canada (Table 4), another evaluation of the annual incidence of rickets in the Manitoba region (Canada) revealed a higher than expected incidence (per 100,000) of 8.2 cases in infants and 1.6 cases in young children (1-7 yrs) [89]. Most of the cases were found in indigenous/Inuit children from poor families. A survey of Southern Denmark (1.3 million inhabitants) identified 214 cases of rickets over a 20-year period. Nearly half of the cases were native Danish

children below the age of 4, whereas all cases above the age of 4 were immigrant children [90]. The incidence of rickets in infants (< 1 yr) in Sweden increased 10 fold over the last 20 years [91]. Indeed, the incidence increased from 2.9 cases per 100,000 in 1997 to 28.7 cases per 100,000 infants in 2014. The major risk factors were prematurity, SGA and foreign-born mothers but in absolute terms the majority of cases were children of Scandinavian origin.

b. Prevalence of severe vitamin D deficiency

The frequency of severe vitamin D deficiency (serum 25OHD < 12 ng/ml or 30 nmol/l) is much higher than the frequency of clinical rickets. This is similar to the discrepancy between (chemical) iodine deficiency and major neurological or mental problems in children (discussed below). An overview of the vitamin D status in different areas of the world revealed that about 7% of the world populations lives with serum 25OHD below 30 nmol/l or 12 ng/ml (reviewed in [92,93]) [94–99]. This risk of poor vitamin D status is higher in certain risk groups such as infants, pregnant women, elderly subjects or immigrants or refugees with a darker skin living in moderate climate. No doubt, that the combination of being an infant from a vitamin D deficient mother with a dark skin living in a moderate climate generates many factors predisposing for severe vitamin D deficiency and its consequences. In many countries around the world serum 25OHD concentrations below 12 ng/ml are frequent in infants and young children, but there is a clear lack of systematic population based studies. The mean serum 25OHD concentrations in countries such as in the Middle-East, the Gulf states, Northern Africa, Northern India, Pakistan and Bangladesh, as well and Northern China and Mongolia are so low that many children fall below 12 ng/ml [100,101].

Prevention of nutritional rickets

There is great consensus around the world how nutritional rickets can and should be prevented.

General consensus guidelines have been updated from time to time over the last decades [102], as to define the optimal vitamin D status at different ages. Special attention was each time devoted on how to prevent rickets. Among the more than 40 different guidelines originating from different governmental or scientific societies, there is virtual unanimity that systematic supplementation of all infants with 400 IU of vitamin D₃ per day can prevent rickets if at the same time sufficient (dependent on the age of the infant or children) calcium intake is guaranteed. This dose of vitamin D is higher than was recommend many years ago (200 IU/d) with equally high success. For older children the Institute of Medicine recommends 600 IU/d and this has been also accepted in other guidelines. Specific documents dealing with rickets provide practical details, including the minimal daily calcium requirements. These recent consensus documents were written by a large team of experts, describing in great detail the practical aspects of diagnosis and treatment [55,56,58–60].

Therefore, we can conclude that far too many children still suffer from nutritional rickets, whereas there are adequate and affordable strategies (albeit adjustable to local circumstances) to prevent this disease. About 90 years ago, the American pioneer in eradicating rickets in North America wrote “... *within the next decade [text written in 1929], or even sooner, it [rickets] will be almost completely eradicated, so that it will become as rare as infantile scurvy since the wide-spread use of orange juice*” [44].

The WHO should lead the way to implement a strategy to eradicate nutritional rickets by 2030.

Several decades ago, iodine deficiency disorders were highly prevalent around the world especially in regions with poor iodine content of the soil such as in regions far from the oceans or with a volcanic surface. Due to an effective combined strategy, especially by systematic government support for iodination of salt, the severity of these deficiency disorders has been drastically reduced. The WHO has been an active player in this action, together with an ambitious science organizations, and above all remains actively involved to assure the cooperation and implementation of this program [103,104].

Vitamin D deficiency in many ways resembles iodine deficiency, as iodine as well as vitamin D are inactive substrates needed to synthesize active hormones (using different families of enzymes) that bind to a nuclear receptor, which then becomes a complex with another nuclear receptor (RXR) and coactivators, and then finally regulates the expression of a large number of genes [7].

Deficiency of iodine or vitamin D is widespread around the world, but more severe in certain areas or in some risk groups. The global frequency of mild or severe iodine deficiency is very similar to that of moderate and severe vitamin D deficiency, both affecting probably more than 1 billion people [7]. Such deficiencies mainly affect infants and young children and severe deficiencies not only have short-term consequences, but also generate severe lifelong sequelae. Indeed, permanent brain damage due to perinatal iodine deficiency is only the tip of an iceberg covering many other more subtle consequences of iodine deficiency. Similarly, nutritional rickets is also only the tip of an iceberg hiding a whole series of less visible consequences of vitamin D deficiency [57].

Correction of iodine or vitamin D deficiency is relatively easy and inexpensive and cost efficient. Correction of both deficiencies, however, requires a nearly permanent and consistent implementation policy, especially since such deficiencies are now affecting mostly the poorest populations or risk groups. Correction of endemic vitamin D deficiency has proven to be possible and highly efficient in eliminating the major health consequences of its deficiency, as demonstrated again and again in most Western countries (already for nearly a century) and more recently in Finland by a well-planned food fortification policy [105,106] and in Turkey by a dedicated health policy planning [86]. A more general policy for ameliorating the vitamin D status has been reported recently by a group of experts [107].

As mentioned above, in 3 large surveys in Canada, New Zealand and the UK, infants and children who regularly have taken vitamin D supplementation were free of rickets, so that the disease was actually mainly affecting the ones that for a combination of reasons need the supplementation more than other children, but in reality do not have access to the simple corrective strategy [107].

For both iodide and vitamin D, excess intake may cause problems of toxicity so that there is need for maintaining a correct balance between sufficient dosing to avoid some residual cases with severe deficiency, while avoiding overdosing causing potentially severe side effects and toxicity.

The endocrine community (especially the International Society of Endocrinology), the bone and mineral societies (under the umbrella of the international Federation of musculoskeletal research societies, IFMRS), the major European and American Pediatric Societies, and the vitamin D community (during the 23th Vitamin D Workshop held in New York City in May 2019) unanimously supported an action plan to prepare a dedicated memorandum to ask the WHO to approve and implement an action plan to “eradicate nutritional rickets by 2030”. This would be fully in line with several WHO action plans to correct micronutrient deficiencies in the world [108,109]. Other major international organizations (such as the Bill and Melinda Gate Foundation, The Thrasher Foundation, UNICEF...) will also be contacted as to support this action plan.

To achieve this goal we made a multistep action plan:

Step 1. Appoint a task force on behalf of the International Society of Endocrinology (ISE), the Federation of Musculoskeletal Research societies (IFMRS), US and European Pediatric Endocrine Societies and the Vitamin D Workshop to prepare a motivated memorandum for WHO. This memorandum should follow the general WHO recommendations to motivate an action plan to change nutritional policies [110]. This includes a chapter on:

- a. Purpose and background of this document**
- b. Diagnostic criteria**
- c. Causes, determinants and consequences**
- d. Magnitude and distribution of condition; nutrient status in populations**
- e. Developing solutions: guidelines and interventions**
- f. Implementation: country-specific policy and translation**

g. Monitoring: frameworks and tools for monitoring and evaluation

h. summary and conclusions OR executive summary

Step 2. The draft version of the memorandum will be evaluated by a team of experts from around the world and from the major international societies so that a final version can be presented in Geneva.

Step 3. Discussion of the memorandum with the leadership of nutritional interventions of the WHO in Geneva. If needed, the Memorandum will have to be adjusted with the WHO general policies.

Step 4. As many WHO member states as possible will be asked to sign a letter requesting the WHO to implement a worldwide strategy to eliminate rickets before 2030. At this stage, the major international societies and their national or regional members will be essential to convey the message at the right time to the right person (generally a governmental organization or health minister). The ultimate aim is to convince these key decision makers of the WHO member states to support and sign such request letter. According to the WHO policy, scientific arguments alone are not sufficient to start nutritional (or other) implementation programs unless asked to take such action by a large number of WHO member states.

Step 5. WHO adds the memorandum and action plan to eradicate rickets on the agenda of the General Assembly of WHO.

Step 6. Approval and implementation of plan to eradicate rickets before 2030

Step 7. Somewhere along the line of the multistep program, other organizations such as UNICEF, the Bill and Melinda Gates Foundation, The Thrasher Foundation will be contacted as to support this action plan.

General summary and conclusions

Nutritional rickets was a major health problem in many European and North American countries. In the early decades of the 20th century, severe vitamin D deficiency was identified as the main cause of this disease of infants and children. Vitamin D supplementation (either as cod liver oil, or synthetic vitamin D₂ or D₃) of all infants during the first year of life was able to (nearly) eliminate nutritional rickets in the Western world. During the 20th century, it became clear that a sufficient (age adjusted) supply of calcium was equally important to a sufficient vitamin D status as to eliminate nutritional rickets. In addition, other causes of rickets, not related to vitamin D or calcium intake were identified and for most children with these rare disorders an appropriate strategy to prevent the consequences of these forms of rickets were found. Today, nutritional rickets is still frequent in some countries or regions of the world or in specific target groups. There is unanimous consensus that nutritional rickets can and should be eliminated by using a well-documented and proven strategy of adequate supply of vitamin D and calcium to all infants and (young) children.

The vitamin D science community and the major international societies dealing with (adult or pediatric) endocrinology, bone or calcium metabolism should take appropriate actions to implement such strategy. The WHO is probably the key international organization to advise and help member states as to implement a strategy to eliminate rickets before 2030. The excellent example of eradication of iodide-deficiency disorders can be the best guide to start such implementation policy.

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Table 1. Historical theories before the discovery of the etiology of nutritional rickets (Based on [111])

<p style="text-align: center;">THE ETIOLOGY OF RICKETS : A CLINICAL AND EXPERIMENTAL STUDY.*</p> <p style="text-align: center;">By LEONARD FINDLAY, M.D.,</p>
<p>Etiology of rickets: unknown but many speculations</p>
<p>Rickets can be induced in dogs by “exercise deprivation”</p>
<p>Black and Italian children nearly always develop rickets when living in NY but not when living in their natural “habitat”</p>
<p>Rickets: disease of temperate zones and urban populations and especially, but not exclusively, in poor families</p>
<p>Rickets in lion cubs and young monkeys of the London Zoo can be prevented by feeding fat and cod liver oil</p>

Table 2. Major milestones in the discovery of the origin of nutritional rickets

1	Sunlight or UV B can cure rickets
1.1	Sniadeck (1822) discussed the cure of rickets and recommended: <i>“Take the children out into the country and deep them in the dry open and pure air”</i> or at least <i>“exposure them to the sun, the direct action of which must be regarded as one of the most efficient methods for the prevention and cure of this disease”</i> (cited by [112]).
1.2	Palm described in the late 19 th century that based on the geographic differences in the prevalence of rickets between Japan or China and London, that sun exposure may be involved and he advocated <i>“sunbathing to treat and prevent rickets”</i> [36].
1.3	Hutchison (UK): Rickets is frequent in children of rich families in British India (Hindus and Muslims) <i>“due to lack of fresh air, sunlight and exercise”</i> [37].
1.4	Huldschinsky (1919): Rickets in children can be cured by artificial UV light (mercury vapor lamp) [38].
1.5	Chick et al. independently also found that rickets in children could be prevented or cured by exposing them to sunlight or to artificially induced ultraviolet light [39], see [34] for reprint).
1.6	Hess : Infantile rickets can be cured by artificial light or sunlight [113]
2	A new vitamin in cod liver oil can cure rickets
2.1	Mellanby demonstrated that dogs developed severe rickets when fed an oatmeal diet resembling that of many Scottish children who are prone to rickets. He kept the dogs indoors and thus deprived from ultraviolet light. In line with McCollum's studies in rats, he demonstrated that cod liver oil could cure rickets in these dogs. He initially thought that vitamin A would be the curing factor [114], see [115] for reprint).
2.2	McCollum (Johns Hopkins, US) discovered that aeration and heating of cod liver oil no longer prevented xerophthalmia due to vitamin A deficiency, but such cod liver oil still could cure rickets. McCollum therefore concluded that cod liver oil contains a new vitamin, called vitamin D as vitamin A, B and C were already known in 1922. Nutritional rickets was therefore considered to be due to a new and heretofore unknown vitamin that became known as vitamin D.
3	Solving the dual origin of the same vitamin: dietary and UVB-induced cure of rickets
3.1	Goldblatt and Soames showed that UVB irradiation of rat livers, taken from rachitic rats, was able to cure rickets [116].
3.2	Steenbock (US, 1924): UV-irradiated vegetable oil can cure rickets (patent of Wisconsin University) [45].
3.3	Hess (US, 1924) independently found that irradiating animals or some food items, could cure rickets [44,46,117]
3.4	Hess and Weinstock (US, 1925): UV irradiation (mercury vapor lamp) of human skin can cure rickets in rats [118].

4 Identification of the structure of vitamin D

- 4.1 The identification of vitamin D₂ was realized independently by **Windaus** [119] and by **Askew** [120] [121]
- 4.2 **Windaus and Bock** isolated 7-dehydrocholesterol, the essential precursor of vitamin D₃ from skin [122]
- 4.3 **Brockman** isolated 2 grams of vitamin D₃ from 150 kg of tuna fish liver oil [47]
- 4.4 **Windaus' group** finally realized the chemical syntheses of the vitamin D compounds, confirming their structures [49]. Windaus received a Nobel prize in 1928 (in fact for his synthesis of vitamin D₃) [123].

Table 3. Prevalence of rickets or vitamin D deficiency in children of non-Western countries

Country	Prevalence or number of cases	Comments	Reference
Korea	35 cases in 2 years in major hospital	Only 51% had serum 25OHD below 15 ng/ml	[124]
China	3,7%	Rural China, based on radiographic examination	[125]
Bangladesh	30 or 13%	Based on one or three clinical signs of rickets, respectively	[126]
Mongolia	9,4 and 25,6% 23,1%	Children below age 5 with craniotabes or X-legs, respectively Serum 25OHD concentration below 7.2 ng/ml	[127]
India	77 and 13%	Serum 25OHD below 12 ng/ml - clinical signs of rickets in Pune	[128]
Turkey	6 and 0,1%	Prevalence in 2005 and 2008, respectively	[129]
Middle-East and North-Africa	27 and 10% 0,5 and 1%	Prevalence in Northern Yemen and rural Egypt, respectively Prevalence in Kuwait and Saudi Arabia, respectively	[101]
Nigeria	0,64 %	Incidence in children aged 1-3 yrs	[130]
The Gambia	1,5 and 0,05 %	Survey of children below age 5, clinical and radiological signs, respectively	[61]

Table 4. Incidence of rickets in Western countries

Country	Incidence per 100.000 persons	Comments	Reference
Canada	2,9 104 cases	Survey of 2325 Canadian pediatricians (2002-2004); mostly breastfed (94%) and with intermediate or dark skin (89%)	[131]
New-Zealand	2,2 for children <15 yrs 10,5 for children <3 yrs	Risk factors: darker skin, Indian or African ethnicity, longterm breastfeeding, winter or spring. None received vitamin D supplements.	[132]
Japan	1,1 for children <15 yrs 3,5 for children <5 yrs	Nationwide survey. Exclusive breastfeeding, inappropriate diet, lack of sun exposure.	[133]
Japan	9 for children <4 yrs		[134]
UK	3,2 for children < 15 yrs (2007-2011)		[135]
Denmark	2,9 for children <5 yrs in 1995-2005 1,7 for children <15 yrs in 1985-1995	74 % of cases were children of ethnic minorities, especially from the Middle-East 88% did not receive vitamin D supplements	[136]
Australia	4,9 for children <15 yrs	98% dark or intermediate skin, 75% born in Africa, 75% refugees. All with serum 25OHD below 20 ng/ml (median 12 ng/ml), majority in Southern "summer and autumn".	[137]