PAN Physicians Association for Nutrition

Practical Guide for Healthcare Professionals

Vitamin B12

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1. What is the scope of this document?

Vitamin B12 is an essential nutrient for the human body. Vegans, vegetarians, and those limiting the intake of animal-based products are at a high risk of B12 deficiency. This guide is aimed at physicians, dietitians, nutritionists, and other healthcare professionals treating people following plant-based diets. It provides some background information about B12, an overview of laboratory indicators to consider, and how to treat and prevent B12 deficiency in people of different ages and physiological statuses.

2. What is vitamin B12, and how does it work?

Vitamin B12 is also called cobalamin as it contains the mineral cobalt. vitamin B12 is synthesised by certain bacteria and archaeons but not by plants or animals (1). Animals accumulate vitamin B12 in their tissues. In omnivore diets, meat, dairy, and other animal-sourced foods are the predominant sources of vitamin B12 (1).

Vitamin B12 is a water-soluble vitamin essential for the human body. It is required for the development, myelination, and function of the central nervous system, synthesis of all blood cells, and DNA synthesis. Vitamin B12 is also needed to create amino acids for protein synthesis.

Vitamin B12 is a cofactor of two enzymes, methionine synthase and L-methylmalonyl-CoA mutase. Methionine synthase converts homocysteine into the essential amino acid methionine. Methionine is required to form S-adenosylmethionine, a universal methyl donor for almost 100 substrates, including DNA, RNA, proteins, and lipids. A vitamin B12 deficiency results in an accumulation of homocysteine, which can harm the human body.

The other enzyme which needs vitamin B12 is L-methylmalonyl-CoA mutase. This converts L-methylmalonyl-CoA to succinyl-CoA in the metabolism of propionate, a short-chain fatty acid (2). B12 deficiency results in elevated methylmalonic acid.

3. What are the dietary sources of vitamin B12 in plant-based diets?

In conventional omnivore diets, vitamin B12 is available from animal-based foods such as meat, liver, fish, eggs, and dairy products. Microorganisms in ruminants' stomachs can synthesise vitamin B12. The cobalt content in ruminants' diet is the most important factor affecting the synthesis of B12 (1). Farmed ruminants (sheep and cows) are often supplemented with cobalt to improve B12 synthesis and B12 content in meat and dairy (1,3–5).

A few plant-based foods, such as tempeh, some edible algae, and a few mushrooms, might contain negligible amounts of vitamin B12 (see Table 3.1 below). Most of these products are often difficult to find and to incorporate into daily diets (6). **Plants are not a reliable source of B12, and those following a diet with little or no animal-based foods are strongly recommended to take vitamin B12 supplements.** Most vegetarians, for example, who include dairy and eggs in their diets, do not obtain enough vitamin B12 for their needs from these foods.

Some plant-based foods, such as plant-based milks, are fortified with vitamin B12 (see Table 3.1 below). However, the fortified product range and their physical and financial accessibility varies from country to country. For example, only 20% of plant-based meats in Australia are fortified with vitamin B12 (7). In Europe, around 40% of plant-based milk products are fortified. Fortification is more frequent in some countries, such as the Netherlands and Belgium and is less common in Germany and Spain (8). In theory, these products could be incorporated into diets, but individuals would need to consume 3-4 portions of fortified products to meet the recommended vitamin B12 intake for adults of 4 µg/day. Of note, organic plant-based milk and meats might not always be fortified with vitamin B12, and it is always best to check the product's label (8).

Given all the issues concerning the availability of fortified plant-based options and their low and variable vitamin B12 content, it is best not to rely on fortified products as the exclusive source of vitamin B12 in plant-based diets. However, these products might be beneficial for plant-based eaters. Evidence shows that small and frequent doses throughout the day (e.g. through fortified foods and supplements) might have a positive role in improving and maintaining an optimal vitamin B12 status.

Table 3.1: Vitamin B12 content in some plant-based foods and alternatives.

Food	Vitamin B12 (per 100g)	Vitamin B12 (per portion)
Dried Nori (purple laver), (9)	77.6 µg	77.6 µg
Tempeh, (10)	0.1 µg	0.1 µg (100g)
Dry shiitake mushrooms, (9)	4.8 µg	2.4 µg (50g)
Fortified soya milk (Switzerland), (11)	0.2 µg	0.3 µg (150ml)
Fortified plant-based meat (Sweden), (12)	0.38 µg	0.38 µg (100g)
Fortified Breakfast cereals (UK), (13)	2.4 µg	0.72 µg (30g)
Yeast extract (UK), (13)	14.5 µg	1.0 µg (7g)

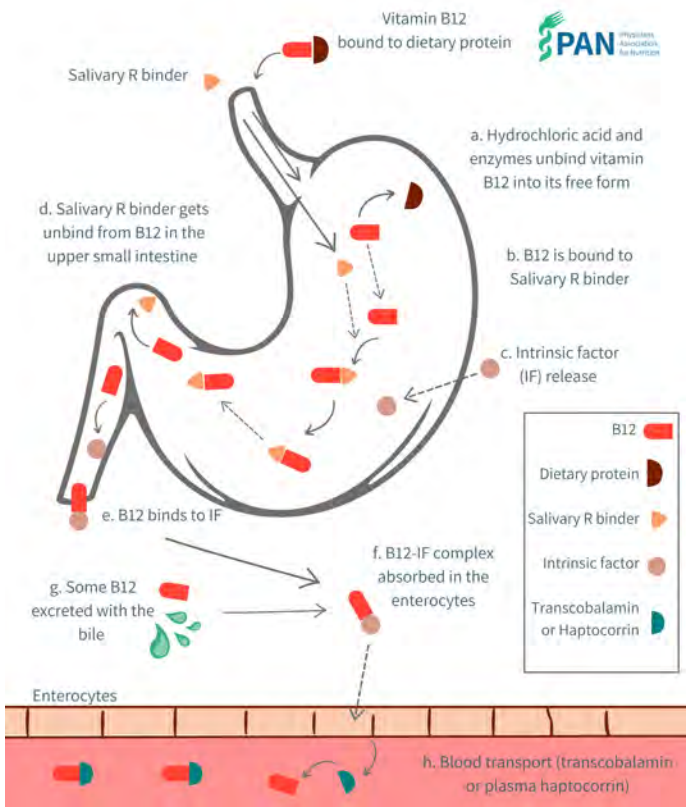
4. How is vitamin B12 absorbed?

Vitamin B12 can be absorbed by passive diffusion and an active physiologic process (Figure 4.1). These processes are crucial to understanding the different causes of vitamin B12 deficiency.

1. **Passive diffusion** - This occurs throughout the surface of the digestive tract. Only 1–2% of vitamin B12 is absorbed passively. Thus, this represents only a small fraction of the vitamin B12 absorbed from food sources (14). Higher absorption occurs when B12 is consumed in supplemental doses (>50 µg). Absorption by passive diffusion can also occur in mucous membranes, including those in the mouth and the nose (14). Absorption by passive diffusion can occur without the intrinsic factor (see paragraph below).
2. **Active physiologic process** (Figure 4.1) - Vitamin B12 is bound to proteins in foods. To be absorbed, vitamin B12 must be released from dietary protein. The process starts in the mouth, where vitamin B12 is mixed with the saliva and where the R-binder is produced. Once in the stomach, hydrochloric acid and enzymes unbind vitamin B12 into its free form (Figure 4.1a). Here, vitamin B12 binds with the salivary R-binder (Figure 4.1b). In the stomach, a protein called intrinsic factor (IF) is released (Figure 4.1c).

In the small intestine, vitamin B12 is unbound from the salivary R binder (Figure 4.1d) and combines with IF (Figure 4.1e) to be absorbed further down the small intestine. The vitamin B12-intrinsic factor is absorbed through specific receptors located on the enterocytes (Figure 4.1f).

Figure 4.1 - Active absorption of vitamin B12 in the digestive system.



- **Plasma transport** - After absorption in the enterocytes, vitamin B12 is then released into the bloodstream, where it is bound to two proteins: plasma haptocorrin and transcobalamin (Figure 4.1h) (14). Plasma haptocorrin transports around 70-80% of total B12, but the vitamin is not available to tissues as only hepatic cells have haptocorrin receptors. Transcobalamin carries 20-30% of the remaining plasma vitamin B12 to all cells for DNA synthesis (14).

- **Enterohepatic circulation** - Another critical component of vitamin B12 absorption is enterohepatic circulation. It is estimated that between 0.5 and 5.0 µg of B12 is excreted in the bile daily (Figure 4.1g). This biliary vitamin B12 is readily reabsorbed in the small intestine. Thus, the enterohepatic circulation represents a mechanism by which the body conserves B12. The biliary B12 reabsorption process is very effective: it may take years to lose substantial amounts of the vitamin through this route and develop a vitamin B12 deficiency. However, in conditions that cause B12 malabsorption (such as pernicious anaemia, an autoimmune disease), vitamin B12 depletion can be very rapid (<1 year)(14).

5. What is the bioavailability of vitamin B12 from foods and supplements?

Studies suggest consuming high doses of B12 can saturate the B12-intrinsic factor receptor in the enterocytes and decrease absorption. There is a refractory period of about 6 hours before the receptors in the gut can be replenished to allow further active absorption of B12. This explains why high oral doses of B12 do not get fully absorbed. Studies show that the percentage of the dose absorbed decreases with increasing amounts of B12 consumed (14). When meals contain more than ~2 µg of vitamin B12, absorption falls to about 20% (15). Therefore, the effective content of vitamin B12 from (animal-based) food sources becomes only 20% of that listed in food composition tables.

Studies using isotopes showed that supplements may have greater absorption than food-based vitamin B12. For example, B12 retention from supplements was estimated at 50% of 1 µg, 20% of 5 µg, and 5% of 25 µg dose (14).

Absorption is about 2% at doses of 500 µg and 1.3% at doses of 1,000 µg (2). Absorption of vitamin B12 from fortified foods such as breakfast cereal is higher (around 60%) than food-based vitamin B12 (14). Small B12 doses throughout the day might be more effective in improving B12 status than high-dose supplements (14,16).

6. How much vitamin B12 is needed each day?

In 2015, the European Food Safety Authority (EFSA) issued vitamin B12 recommendations (as Adequate Intakes) for different age groups (17). In its recommendations (Table 6.1), EFSA noted consistent evidence from observational and intervention studies that a vitamin B12 intake of 4 µg/day and greater is associated with serum concentrations of vitamin B12 markers observed in healthy adults (17).

Table 6.1 Recommendations (as Adequate Intakes) for vitamin B12 in different age groups according to the European Food Safety Authority.

Age group	Adequate Intake (µg/day)
7-11 months	1.5
7-3 years	1.5
4-6 years	4.5
7-10 years	2.5
11-14 years	3.5
15-17 years	4
≥18 years	4
Pregnancy	4.5
Lactation	5

7. How much is too much?

No toxic effects of vitamin B12 have been identified, even when administered at 300–3000 times the recommended dietary allowance, as only a small fraction of the vitamin is absorbed at supplemental doses (18). For this reason, no tolerable upper intake level has been set (15).

8. Which are the populations at risk of deficiency?

Older adults. B12 deficiency affects **20% of the elderly population** in high-income countries (regardless of their diet) (19). This is because the capacity of vitamin B12 absorption is reduced with age.

People with pernicious anaemia. This disease **affects 0.1% of the general population** and 1.9% of the elderly. Pernicious anaemia represents 20–50% of the causes of vitamin B12 deficiency in adults (20). It arises due to autoimmune gastritis, a chronic inflammatory disease affecting the part of the stomach producing intrinsic factors. The lack of intrinsic factors in patients with pernicious anaemia causes B12 deficiency through malabsorption of both dietary and recycled biliary B12, resulting in progressive exhaustion of B12 reserves in the body (15).

People with gastrointestinal conditions and surgeries. Gastrectomy, gastric bypass, chronic gastritis, Helicobacter Pylori infection, pancreatic insufficiency or pancreatectomy, ileal resection, chronic diarrhoea, parasitic infestation and bacterial overgrowth can cause or increase the risk of vitamin B12 deficiency (15).

People on vegan, vegetarian and plant-based diets. Without adequate intake through supplements or adequate intake of fortified foods, these groups are at a high risk of developing B12 deficiency over time (14,15,21). Some surveys showed that in some contexts, vegans, vegetarians and those following a plant-based diet do not always take the recommended vitamin B12 supplements (22–24).

Infants of vegan mothers. Exclusively breastfed infants of women who consume no animal products might have very limited reserves of vitamin B12 and can develop vitamin B12 deficiency, sometimes very early in life (15,25). If the mother is vitamin B12 depleted, very small amounts of vitamin B12 will cross the placenta during foetal development (2). Vitamin B12 content in breast milk is highly correlated with maternal status and storage of vitamin B12 (15). Most commercially prepared infant formulas are enriched with B12 up to concentrations of 800–1,200 pmol per litre (14).

Prolonged intake of some drugs. Widely used drugs affecting gastric acid secretion, such as proton-pump inhibitors (e.g. omeprazole) and antacids, may interfere with food-based B12 absorption (15). Evidence shows that in some countries, up to 30% of the adult population regularly takes these drugs (26). Other widely used drugs include histamine H2 receptor antagonists, colchicine, and metformin (27). The latter is prescribed to more than 80% of diabetic patients (28). Chronic anaesthetic gas nitrous oxide exposure can cause a functional B12 deficiency (14,29).

Some populations from low and middle-income countries. In countries where animal-based food intake is very low (5-10% of the total energy), such as Kenya and India, low and marginal vitamin B12 status is very prevalent (more than 50% of the population showing low serum B12) (14).

9. What are the symptoms of vitamin B12 deficiency?

Neurological manifestations. Vitamin B12 deficiency affects the nervous system, resulting in demyelination of peripheral and central neurons. This leads to peripheral neuropathy (often presenting as tingling or numbness in hands or feet), dementia, poor cognitive performance, and depression (15). Evidence suggests that the neurological manifestations of B12 deficiency can precede the appearance of haematological changes and may even occur in the absence of any haematological complications (15). In infants and children, the neurological manifestations include a wide variety of symptoms, such as slow growth and developmental delays (30). During foetal development, low maternal B12 status has been linked to an increased risk of neural tube defects (in populations with and without folic acid fortifications) (15).

Haematological manifestations. The haematological effect of B12 deficiency is megaloblastic or macrocytic anaemia (large red blood cells), which results from disruption of DNA synthesis (15,31). Neutrophil hypersegmentation is another manifestation of B12 deficiency (31).

Other manifestations. include sore tongue or mouth, fatigue, weight loss, loss of appetite, increased risk of bone loss, and macular degeneration (15).

10. How to assess vitamin B12 status?

No single vitamin B12 biomarker provides sufficient specificity and sensitivity to diagnose B12 deficiency (14). Several blood biomarkers should be used in conjunction with clinical findings. The blood biomarkers are:

- Serum (or plasma) vitamin B12 concentration
- Serum holo-transcobalamin (holoTC) concentration
- Serum methylmalonic acid (MMA) concentration
- Plasma homocysteine (tHcy) concentration.

There are no gold standards in cut-off values for B12 biomarkers for defining status (14,15).

Commonly used cut-offs can vary and are somewhat controversial due to the high prevalence of subclinical B12 deficiency and limited data linking these to functional outcomes (14). **It is worth noting that cut-off values for biomarkers for infants, children, and pregnant women differ from those for the general population** (see Table 10.1).

Furthermore, laboratory "normal" ranges for B12 adequacy and test specificities and sensitivities vary (32,33). Reference values and cut-offs should be interpreted cautiously, particularly when assessing infants, children, and pregnant women. Often, laboratories do not offer values for different age groups and pregnancy. Table 10.1 below summarises the laboratory cut-offs to consider in different groups.

Table 10.1. Laboratory indicators to assess vitamin B12 status

Vitamin B12 measures, unit	Details	Commonly Used Cut-off values * (14)
Serum/ plasma B12, pmol/L	Reflects both intake and stores; however, blood values may be maintained while tissue stores become depleted; best when combined with holoTC or MMA to improve predictive value (31). Influenced by: Mid-pregnancy may decrease values 20-30% but do not indicate depletion; values fall between birth and 6 months and then increase; not affected by ageing or infection; lower concentrations in smokers and with alcohol. It may be lower with large vitamin C doses, inherited benign haptocorrin deficiency, and low folate status (31). **The serum B12 measure is relatively cheap and widely available.** Serum B12 is also not a sensitive marker of functional B12 status. False positive and negative results are common (31). Fasting is not required as values are not significantly affected by recent intake. Sample collection and processing factors can affect values. Note that while serum B12 values might fall in the range of normality, other biomarkers might indicate a B12 deficiency. It is a common practice among dietitians and healthcare professionals to aim for plasma B12 to be around 400-500 pg/ml. This ensures a sufficient margin of safety and adequate B12 levels for optimal health.	• Adults ○ adequate >221 ○ depleted ≤ 221 (≤300 pg/mL) ○ deficient < 148 (<200pg/mL) • Infants ○ Newborn cord blood 120-690 ○ 6mo 121 – 520 ○ 12mo 165 – 580 ○ 24 mo 183 – 260 • Children, adolescents (34) ○ 3 – 5 yr 423 – 996 ○ 6 – 12 yr 203 – 901 ○ 13 -18 yrs 113 – 458 [Also reported RI (35)] ○ 1 - 11 yr 260 – 1200 ○ 12 – 18 yr 200 – 800 Note that 1.0 pg/mL = 0.7378 pmol/L

Vitamin B12 measures, unit	Details	Commonly Used Cut-off values * (14)

Serum holo-transcobalamin (holoTC), pmol/L	holoTC delivers B12 to cells and is the functionally important "active B12" fraction of blood (vs haptocorrin-bound B12); holoTC best reflects recent intake and absorption and is a sensitive marker for early insufficiency; predictive value improves when combined with serum total B12 or MMA (36). **Serum holoTC can be expensive and not widely available.**
	
	Pregnancy does not change serum holoTC values; low in infants ~6 months; not affected by infection; chronic kidney disease elevates but less so than other markers. Can be used to test malabsorption.
	
	Fasting is not required. Serum recommended as EDTA for plasma increases values in some studies.
		• Adults
		  ○ adequate 40 – 150
		  ○ deficient < 35 – 40
		• Adequate infants
		  ○ Newborn (cord blood) 33-240
		  ○ 6mo 12 – 90
		  ○ 12mo 19 – 100
		  ○ 24 mo 29 – 110
		• Children, adolescents (34)
		  ○ 3 – 5 yr: 63.6 – 226.4
		  ○ 6 – 12 yr 48.1 – 180.2
		  ○ 13 -18 yr 32.6 – 113.3

Serum methyl-malonc acid (MMA nmol/L	Serum (and urinary) MMA is the most sensitive indicator of deficiency (2,18) and reflects liver stores and functional B12 status but not recent intake. **Serum and urinary MMA is expensive and not widely available.** (18).
	
	Influenced by: Normal renal function (creatinine testing is required). Antibiotic use/bacterial flora/overgrowth may increase values.
	Serum MMA increases with B12 deficiency, is reduced ~15% in pregnancy, elevated in infants ~6 mo of age, and increases with ageing (>50y, especially >70y), tends to be higher in low-income populations independent of B12 status (possibly due to microbiome differences).
	
	Fasting is not required but several high doses in 24 h may increase values.
	
	Note elevated serum MMA alone is not proof of B12 deficiency(36); has a low diagnostic specificity with marginally elevated levels; ancillary measurements to support the diagnosis and therapeutic response to treatment are needed (31).
	Urinary MMA is also a sensitive indicator and increases with B12 deficiency; values need to be corrected for creatinine; urinary MMA increases after a meal.
		Serum MMA:
		• Adults:
		  ○ adequate (likely) 120
		  ○ deficient > 281
		• Infants:
		  ○ Newborn (cord blood) 170-500
		  ○ 6mo 140 – 220
		  ○ 12mo 120 – 830
		  ○ 24 mo 120 – 300
		• Children, adolescents (34)
		  ○ 3 – 5 yr 98 – 345
		  ○ 6 – 12 yr 117 – 378
		  ○ 13 -18 yr 112 – 348
		
		Values often increase when serum B12 <287 pmol/L
		
		Urinary MMA/creatinine >3.6mmol/ml has been reported as the cut-off for "elevated" in adults from developed countries (35).

Plasma total homocysteine (tHcy), µmol/L	A relatively sensitive but not a specific indicator of B12 status. May distinguish between folate and B12 insufficiencies. tHcy concentrations rise in both folate and vitamin B-12 deficiencies. But only B12 deficiency will make MMA rise (36). However, see confounders listed for both. Affected by folate, B6, B2, health conditions (2) (e.g. hypothyroidism, pre-eclampsia), MTFR enzyme polymorphisms, renal function (2,36), recent high-protein meal, many medications (e.g., methotrexate, L-dopa, metformin, oestrogen), insulin (type 1 diabetes often reduces), oestrogen (menopause increases),	• Adults: Plasma tHcy >12 and >15 have been used to define elevated tHcy (33,36) May increase with serum B12 <300 pmol/L. • Infants: ≥6.5 (15,37)

Vitamin B12 measures, unit	Details	Commonly Used Cut-off values * (14)
Plasma total homocysteine (tHcy), µmol/L (continued)	fasting time. May increase with moderate to severe B12 deficiency, with smoking, age, and endurance training; reduced by ~39% in pregnancy. **Plasma tHcy is relatively cheap and widely available.** Plasma is recommended (serum can increase concentrations by release from RBCs).	
Hematologic & neurologic assessments	Includes megaloblastic anemia,(1) neutrophil hypersegmentation, leukopenia; nerve conduction velocity, vibratory sensations, abnormal gait, peripheral neuropathy, and MRI detecting loss of white matter in the spinal cord and brain (2).	

* There is uncertainty in cut-offs used to diagnose deficiency, and values may not have universal agreement among experts.

In summary, **vitamin B12 insufficiency may include one or more of the following** (14):

- ↓ serum holoTC (transcobalamin) and serum B12
- ↑ plasma methylmalonic acid (MMA) and urinary MMA excretion
- ↑ plasma homocysteine (tHcy)
- Hypersegmentation of nuclei in neutrophils
- Megaloblastic anaemia (MCV, Hg, large RBC)

Note: Folate and vitamin B12 share common metabolic pathways and should also be considered when assessing vitamin B12 status. A high folate intake (more than 1000 µ/day) might mask some of the signs and symptoms of vitamin B12 deficiency, such as megaloblastic anaemia (15,31). This phenomenon is called the "folate trap" and can cause functional folate deficiency by "trapping" folate-dependent enzymes in an unusable form (14). Iron deficiency can mask macrocytosis due to B12 deficiency and may need to be considered (31).

Clinical symptoms may occur with adequate haematological markers and vice-versa (14,15). **Therefore, the broad clinical picture must be taken into account when diagnosing vitamin B12 deficiency (14).** Treatment should not be delayed to avoid permanent neurological damage when discordant agreement between strong clinical features and haematological values occurs (18).

It is important to monitor vitamin B12 status in those following plant-based diets, particularly during pregnancy, lactation, infancy, and childhood, to avoid irreversible damage from vitamin B12 insufficiency (14,38).

11. How to treat vitamin B12 deficiency?

Treatment of symptomatic B12 deficiency, resulting from pernicious anaemia or other malabsorptive conditions, requires a different strategy from treating a dietary deficiency. Repeated follow-ups to confirm the efficacy of treatment are also needed (14).

In general, the standard therapy for the correction of vitamin B12 deficiency due to malabsorption disorders consists of an intramuscular injection of 1000 µg cyanocobalamin (or hydroxocobalamin), which can be repeated monthly in accordance with the results of the blood tests (14,15). This is a quick and effective way of delivering a large quantity of vitamin B12 when suspecting a moderate-severe B12 deficiency. In people with mild insufficiency of B12 due to low intake of animal-based foods, oral supplementation has been shown to be as effective as intramuscular administration (14).

This is very useful since intramuscular administration can be painful and expensive for the patient (39). However, studies show that supplementation must occur over several months to address the deficiency (14,38).

The suggested oral dose varies according to the severity of the B12 deficit assessed through blood tests (see paragraph on measures of vitamin B12). **Studies report that a multitude of daily doses are effective in treating dietary deficiency**. A study showed that, in adults, a mild deficiency can be treated with a daily dose of 50 µg of cyanocobalamin over a period of 3 months (40). Another study carried out in India (where B12 deficiency is very prevalent) showed that a very small oral dose of cyanocobalamin (2 or 10 µg) can reduce hyperhomocysteinemia in 4 months (41). In most cases, physicians prescribe supplements at a dosage available in their area. For this reason, it is common to hear treatments consisting of supplementation with daily doses of 100 µg, 500 µg or even 1000 µg.

In children and pregnant and lactating women, the suggested oral dose and schedule (to be implemented in four months) for treating vitamin B12 insufficiency/deficiency when serum B12 is < 75 pmol/L is reported in Table 11.1 below. For serum B12 values between 75 pmol/L and 300 pmol/L, please consider the full algorithm by Baroni and colleagues (38).

Table 11.1. Treatment for B12 insufficiency when serum B12 is < 75 pmol/L in children and pregnant and lactating women. The below doses are recommended for a period of 4 months (38).

Age group	Dose
6 months to 3 years	A daily single dose of 250 µg or 3 daily doses of 10 µg
4-6 years	500 µg 4 times/week
7-10 years	500 µg 6 times/week
11+ years	1000 µg/day
Pregnancy and lactation	1000 µg/day

12. How to prevent vitamin B12 deficiency?

For diets that are low in or do not include animal-based foods, a daily supplement of 50-100 µg or 1000 µg of vitamin B12 twice a week is recommended to prevent deficiency in healthy adults (39,42). Older adults might need a higher dosage due to poorer absorption.

Daily supplementation of sublingual 1000 µg in older adults is considered appropriate (43,44). The recommended doses for preventing deficiency in infants, children, and pregnant and lactating women are reported in the table below (19).

Table 12.1. Vitamin B12 doses for children and pregnant and lactating women with normal B12 levels to maintain adequacy, as suggested by Baroni and colleagues (38).

Age group	Daily single dose	Daily multiple dose*	Weekly dose
6 months to 3 years	5 µg	1 µg × 2	-
4-10 years	25 µg	2 µg × 2	-
11+ years	50 µg	2 µg × 3	1000 µg × 2
Pregnancy and lactation	50 µg*	2 µg × 3	1000 µg × 2

* Dividing the dose can increase the bioavailability of B12.

Determining the exact dosage to prevent deficiency based on current scientific knowledge is challenging, and very few guidelines are available (16,38). Nevertheless, prolonged high intakes of this water-soluble vitamin do not typically result in negative side effects (18). Most supplements contain a much higher dose than the recommended daily intake as not all the vitamin B12 consumed or ingested is absorbed and utilised by the human body (14). It is recommended to use vitamin B12 as a separate supplement (particularly during pregnancy and lactation when multivitamins and mineral supplements are frequently used). Research has shown that combining it with other nutrients (in multivitamin supplements) can have unintended effects on the quality of vitamin B12 (39).

Daily supplements are better than large weekly doses (38). Studies showed that oral and sublingual supplements are equally effective in preventing B12 deficiency (45).

13. Which supplements to recommend?

Four vitamin B12 forms — cyanocobalamin, hydroxocobalamin, adenosylcobalamin, and methylcobalamin — are currently used for supplementation (46). All four authorised vitamin B12 forms are reported as effective in improving levels in the human body (47), although some individuals seem to absorb some forms better than others (46). There is no advantage to using the light sensitive forms of cobalamin, such as methylcobalamin or adenosyl-cobalamin, instead of the stable cyanocobalamin or hydroxocobalamin, which are readily converted in the body into the active forms (47). Cyanocobalamin is the cheapest and most popular as it is more stable in both supplements and when added as a food fortifier (48,49). Limited evidence suggests that cyanocobalamin might be unsuitable for supplementation among smokers, as it represents a form preferentially excreted for the purpose of hydrocyanic acid removal. Hydroxycobalamin might thus be desirable to treat B12 deficiency in these patients. However, more evidence is needed (39).

Some experts advise buying supplements compliant with good manufacturing practices (GMP). GMP-certified status supplements prove that supplements meet the highest standards for manufacturing products regulated by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (50).

Apart from chewable or sublingual tablets, supplements are also available as pills to swallow or as drops and sublingual sprays, particularly useful for B12 supplementation in children (51).

Some experts recommend taking B12 supplements with an empty stomach (49), while others recommend taking the supplement with food (42,50). This might change according to the type of supplement chosen. Sublingual supplements are absorbed passively and might be taken without food. Oral supplements might need to be taken with food as the release of intrinsic factors is needed for their absorption. It is recommended to check the instructions on the supplement label.

PAN's position statements on vitamin B12

B12 deficiency can result in serious health issues such as permanent nerve damage and haematological conditions. The signs of vitamin B12 depletion may take years to develop after the adoption of diets containing little or no animal-based foods.

- PAN strongly recommends using a vitamin B12 supplement in people consuming little to no animal-based foods (such as vegetarians) and for all older adults. Individuals at high risk should take the appropriate daily or weekly supplements based on their vitamin B12 status, lifestyle, accessibility and preferences.
- PAN also encourages the consumption of healthier fortified foods with vitamin B12 as part of a whole-food plant-based diet, as these foods can be a complementary source of this important vitamin.
- Healthcare professionals should recommend regular check-ups to investigate vitamin B12 status in patients consuming plant-based diets.

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PAN International - Physicians Association for Nutrition was founded in 2018 in Munich, Germany. PAN is a fast-growing international non-profit organisation of medical doctors and healthcare professionals with a bold mission: change the way the world eats in order to improve personal health, prevent diseases and reduce the dramatic numbers of diet-related deaths. With our student network, national offices and campaigns, we bring education, change and motivation for more whole food plant-based eating, to healthcare systems and communities around the world.

We're building a global community of medical doctors, students and healthcare professionals who are committed to transforming the perception, knowledge, and use of science-based nutrition in healthcare and beyond. We do this by providing education, empowerment, and engagement to medical professionals, students, the general public and policymakers towards healthier and more sustainable food for all.

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