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2 **NATIONAL INSTITUTE FOR HEALTH AND CARE**
3 **EXCELLENCE**

4 # Guideline

5 # Vitamin B12 deficiency in over 16s: diagnosis
6 # and management

7 ## Draft for consultation, July 2023

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This guideline covers the diagnosis and management of vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. The guideline includes recommendations on how to identify, test and treat vitamin B12 deficiency based on its cause and monitoring for complications. It aims to raise awareness of the condition in people aged 16 and over, including those who are pregnant or breastfeeding, leading to better diagnosis, treatment and ongoing care. We have used specific inclusive language (pregnant women and pregnant people) to describe this population.

**Who is it for?**

- Healthcare practitioners
- Commissioners of health and social care services
- People with suspected or confirmed vitamin B12 deficiency, including deficiency caused by autoimmune gastritis

**What does it include?**

- the recommendations
- recommendations for research
- rationale and impact sections that explain why the committee made the recommendations and how they might affect practice
- the guideline context.

Information about how the guideline was developed is on the guideline's webpage. This includes the evidence reviews, the scope, details of the committee and any declarations of interest.

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# Contents

# Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

The term 'autoimmune gastritis' is used throughout this guideline. Autoimmune gastritis is a chronic inflammatory disease that destroys parietal cells in the stomach. The consequence of this is vitamin B12 deficiency, and this can lead to pernicious anaemia.

## 1.1 Information and support

1.1.1 When providing information and support to people with suspected or confirmed vitamin B12 deficiency (and their families and carers, if appropriate), follow the advice on:

- knowing the patient as an individual, essential requirements of care and enabling patients to actively participate in their care in NICE's guideline on patient experience in adult NHS services
- putting shared decision making into practice in NICE's guideline on shared decision making
- supporting decision making in NICE's guideline on decision making and mental capacity.

1.1.2 Explain to people with suspected vitamin B12 deficiency (and their families and carers, if appropriate) that:

- the symptoms and signs associated with vitamin B12 deficiency are also linked to many other conditions

- it can be difficult to find a specific medical cause for some symptoms, such as fatigue
- most people only need 1 blood test to diagnose vitamin B12 deficiency but some may need further tests.

1.1.3 Explain to people with confirmed vitamin B12 deficiency (and their families and carers, if appropriate) that:

- vitamin B12 deficiency affects each person differently and has various causes
- the condition can affect daily activities, family and social life, work and education
- treatment with vitamin B12 replacement is effective in most people
- for some, the dose, frequency and route of administration may need to be adjusted for it to work properly
- it is important to continue with treatment so symptoms do not return or get worse
- some causes of vitamin B12 deficiency will need (and receive) lifelong treatment, such as deficiency caused by autoimmune gastritis.

1.1.4 Explain to pregnant women and pregnant people who are receiving vitamin B12 replacement that using nitrous oxide with air (gas and air) during labour is unlikely to make their vitamin B12 deficiency worse.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on information and support.

Full details of the evidence and the committee's discussion are in evidence review A: information and support.

## 1.2 Recognising vitamin B12 deficiency

### When to test

1.2.1 Offer an initial diagnostic test for vitamin B12 deficiency to people who have:

- at least 1 symptom or sign (see the section on symptoms and signs)
  **and**
- 1 or more risk factors for the condition (see the section on risk factors).

1.2.2 Use clinical judgement when deciding whether to test people who have at least 1 symptom or sign but no risk factors (see the section on symptoms and signs).

1.2.3 Do not rule out a diagnosis of vitamin B12 deficiency based solely on the absence of anaemia or macrocytosis.

See the recommendations on initial tests.

### Symptoms and signs

1.2.4 Be aware that symptoms and signs of vitamin B12 deficiency:

- can vary from person to person **and**
- are often not exclusive to vitamin B12 deficiency.

1.2.5 Recognise that the symptoms and signs listed in box 1 can suggest a vitamin B12 deficiency.

**Box 1**

**Symptoms and signs of possible vitamin B12 deficiency**

- abnormal findings on a blood count such as anaemia or macrocytosis
- cognitive difficulties, including symptoms related to delirium or dementia
- eyesight problems related to optic nerve dysfunction:
  - blurred vision
  - optic atrophy
  - visual field loss (scotoma)
- glossitis
- mental health problems including:
  - anxiety
  - depression
  - psychosis
- neurological or mobility problems related to peripheral neuropathy, or to central nervous system disease including myelopathy (spinal cord disease):
  - impaired balance and falls linked to sensory ataxia (a sign of spinal cord damage that affects proprioception, that is the person's ability to sense movement, action and location)
  - impaired gait
  - pins and needles or numbness (paraesthesia)
- symptoms or signs of anaemia that suggest iron treatment is not working properly during pregnancy or breastfeeding
- unexplained fatigue.

## Risk factors

1.2.6 Identify whether any factors associated with a higher risk of vitamin B12 deficiency are present (see box 2).

1.2.7 Take into account that vitamin B12 deficiency is likely in people after major gastric resections, such as total gastrectomy, if they are not receiving either oral or intramuscular vitamin B12 replacement.

**Box 2**

**Common risk factors for vitamin B12 deficiency**

- age (especially in people aged 65 and over)
- diet low in vitamin B12 (without the regular use of over-the-counter supplements), for example, in people who:
  - follow a diet that excludes, or is low in, animal-source foods (such as a vegan diet, or diets excluding meat for religious beliefs)
  - find it difficult to buy or prepare food (for example, people who have dementia or frailty or those with mental health conditions)
  - have a restricted diet (for example, because of an eating disorder)
- family history of vitamin B12 deficiency or an autoimmune condition
- health conditions:
  - atrophic gastritis affecting the gastric body
  - coeliac disease or another autoimmune condition (such as thyroid disease, Sjögren's disease or type 1 diabetes)
- medicines:
  - the antiseizure medicines phenobarbital, pregabalin, primidone and topiramate
  - colchicine
  - $H_2$-receptor antagonists
  - metformin (see the MHRA safety advice on metformin and reduced vitamin B12: new advice for monitoring patients at risk)
  - proton pump inhibitors
- previous abdominal or pelvic radiotherapy
- previous gastrointestinal surgery:
  - many bariatric operations (for example, Roux-en-Y gastric bypass or sleeve gastrectomy)
  - terminal ileal resection
- recreational nitrous oxide use.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on recognising vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review B: risk factors and symptoms and signs.

## 1.3 Diagnosing vitamin B12 deficiency

### Initial tests

1.3.1 Use either total B12 (serum cobalamin) or active B12 (serum holotranscobalamin) as the initial test for suspected vitamin B12 deficiency unless:

- the test needs to be done during pregnancy or breastfeeding, **or**
- recreational nitrous oxide use is the suspected cause of deficiency.

1.3.2 Use active B12 as the initial test for suspected vitamin B12 deficiency during pregnancy and breastfeeding.

1.3.3 If a person has suspected vitamin B12 deficiency caused by recreational nitrous oxide use:

- use homocysteine as the initial test **or**
- if the test is not available in primary care, refer them to secondary care to have it.

1.3.4 Take blood samples for diagnostic tests before starting vitamin B12 replacement.

1.3.5 Do not delay vitamin B12 replacement while waiting for the test results of people with suspected severe megaloblastic anaemia or sub-acute combined degeneration of the spinal cord.

1.3.6 When offering an initial diagnostic test to a person who is already taking an over-the-counter supplement that contains vitamin B12, ask them what dosage they are taking.

## Factors that can affect initial test results

1.3.7 Use caution when interpreting the test results of anyone who is:

- already taking an over-the-counter supplement containing vitamin B12
- pregnant
- breastfeeding
- taking the contraceptive pill.

## Thresholds for initial test results

### Confirmed deficiency

1.3.8 Diagnose vitamin B12 deficiency in people with any of these test results:

- a total B12 of less than 180 nanogram per litre (133 pmol per litre)
- an active B12 of less than 25 pmol per litre if they are not pregnant or breastfeeding
- an active B12 of less than 35 pmol per litre if they are pregnant or breastfeeding.

1.3.9 When interpreting homocysteine test results, use clinical judgement to determine what reference range to use.

### Indeterminate test results

1.3.10 Consider a follow-up test to measure methylmalonic acid (MMA) concentrations in people who have symptoms or signs of vitamin B12 deficiency and any of these indeterminate test results:

- a total B12 between 180 and 350 nanogram per litre (between 133 and 258 pmol per litre)
- an active B12 of between 25 and 70 pmol per litre if they are not pregnant or breastfeeding
- an active B12 of between 35 and 70 pmol per litre if they are pregnant or breastfeeding.

1.3.11 For people from a Black family background:

- take into account that they may have a higher reference range for serum vitamin B12 concentrations than people from White or Asian family backgrounds
- think about offering treatment, with or without doing an MMA test, if they meet the criteria in recommendation 1.3.10.

1.3.12 Consider treatment, with or without doing an MMA test or waiting for an MMA test result, if the person's initial test result is indeterminate and they meet any of the following criteria:

- they have a condition or symptom that may deteriorate rapidly and have a major effect on quality of life (for example, neurological or haematological conditions like ataxia or anaemia)
- they are aged 65 or over and have cognitive impairment
- they have a condition or suspected condition that increases the likelihood of irreversible vitamin B12 deficiency (for example, autoimmune gastritis)
- they have had surgery that is likely to lead to irreversible vitamin B12 deficiency (such as a gastrectomy, terminal ileal resection or some types of bariatric surgery)
- they are pregnant or breastfeeding.

1.3.13 For people with an indeterminate test result and no symptoms or signs of vitamin B12 deficiency, consider repeating the initial test in 6 months' time, or sooner if they develop symptoms or signs of deficiency.

**Test results indicating vitamin B12 deficiency is unlikely**

1.3.14 Explain to the person that they are unlikely to have vitamin B12 deficiency if they have either of these test results:

- a total B12 of more than 350 nanogram per litre (258 pmol per litre) **or**
- an active B12 of more than 70 pmol per litre, including during pregnancy and breastfeeding.

1.3.15 If the person's initial test result suggested vitamin B12 deficiency was unlikely but they are still experiencing symptoms or signs 3 to 6 months later, consider:

- a repeat of the initial test **or**
- an MMA test.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on diagnosing vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review C: diagnosis.

## 1.4 Identifying the cause of vitamin B12 deficiency

1.4.1 Consider an anti-intrinsic factor antibody test for people with vitamin B12 deficiency if autoimmune gastritis is suspected and they have not previously had:

- a positive anti-intrinsic factor antibody test at any time **or**
- an operation that could affect vitamin B12 absorption (such as total gastrectomy, terminal ileal resection or some types of bariatric surgery).

1.4.2 If vitamin B12 deficiency is diagnosed during pregnancy or breastfeeding and autoimmune gastritis is the suspected cause:

- offer an anti-intrinsic factor antibody test **and**
- start treatment with vitamin B12 replacement in line with recommendation 1.5.3 in the section on managing vitamin B12 deficiency caused by malabsorption without waiting for the test result.

1.4.3 If autoimmune gastritis is still suspected despite a negative anti-intrinsic factor antibody test, consider further investigations such as:

- an anti-gastric parietal cell antibody test
- a test to measure gastrin levels

- a CobaSorb test to measure vitamin B12 absorption
- gastroscopy with gastric body biopsy.

1.4.4 Offer serological testing for coeliac disease where the cause of vitamin B12 deficiency is still unknown after further investigations (see the recommendations on recognising coeliac disease in the NICE guideline on coeliac disease).

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on identifying the cause of vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review D: identifying cause.

## 1.5 Managing vitamin B12 deficiency

1.5.1 At the start of treatment, give people information about:

- how long it usually takes for treatment to take effect **and**
- when they are likely to see an improvement in their symptoms.

1.5.2 Continue with vitamin B12 replacement if treatment was started before pregnancy or breastfeeding.

### Vitamin B12 deficiency caused by malabsorption

1.5.3 Offer lifelong intramuscular vitamin B12 replacement to people if autoimmune gastritis is the cause, or suspected cause, of vitamin B12 deficiency.

1.5.4 In people who have a vitamin B12 deficiency caused by a major gastric resection, terminal ileal resection or a bariatric operation (such as a Roux-en-Y gastric bypass or sleeve gastrectomy):

- offer lifelong vitamin B12 replacement **and**
- consider intramuscular instead of oral vitamin B12 replacement.

1.5.5 If the person has a vitamin B12 deficiency because of malabsorption that is not caused by autoimmune gastritis or surgery (for example, malabsorption caused by coeliac disease), offer either intramuscular or oral vitamin B12 replacement, based on the person's preference.

### Medicine-induced vitamin B12 deficiency

1.5.6 For people with vitamin B12 deficiency that is a side effect of taking medicine:

- offer either intramuscular or oral vitamin B12 replacement, based on clinical judgement and the person's preference, while they are taking the medicine causing the side effect, **and**
- review the need for continuing or changing the medicine that is causing the side effect, where appropriate.

In July 2023, this was an off-label use of intramuscular vitamin B12 replacement. See NICE's information on prescribing medicines.

1.5.7 Review the need for vitamin B12 replacement if the medicine causing the side effect is stopped or the person no longer has symptoms of vitamin B12 deficiency.

### Nitrous oxide-induced deficiency

1.5.8 Offer either intramuscular or oral vitamin B12 replacement to people with a vitamin B12 deficiency caused by nitrous oxide, based on the person's preference.

In July 2023, this was an off-label use of intramuscular vitamin B12 replacement. See NICE's information on prescribing medicines.

1.5.9 If a person's vitamin B12 deficiency is caused by recreational nitrous oxide use, advise them to stop using the substance.

### Dietary vitamin B12 deficiency

1.5.10 If the person is suspected of having vitamin B12 deficiency linked to their diet:

- ask them about their diet
- ask if they are taking, or planning to take, any over-the-counter supplements containing vitamin B12 (see recommendation 1.5.13)
- check whether they have any symptoms, signs or risk factors that could suggest another cause of vitamin B12 deficiency
- be aware that diet (for example, a vegetarian or vegan diet) may not be the cause, or the only cause, of a person's vitamin B12 deficiency.

1.5.11 Consider further investigations to explore other causes of vitamin B12 deficiency if, during discussions, the person suggests or gives information that raises suspicion that the deficiency is not linked to their diet (see the section on identifying the cause of vitamin B12 deficiency).

1.5.12 If the person is taking, or plans to take, over-the-counter supplements:

- explain that supplements contain varying amounts and types of vitamin B12 **and**
- advise them to pick an oral supplement that contains 1 of the following types of vitamin B12:
  - cyanocobalamin
  - hydroxocobalamin
  - methylcobalamin
  - adenosylcobalamin.

1.5.13 If the person has suspected or confirmed vitamin B12 deficiency because their diet is lacking in vitamin B12:

- tell them where to find information on how to improve their intake of the vitamin including information about sources of vitamin B12 in food (see the NHS webpage on B vitamins) **and**
- consider oral vitamin B12 replacement unless they meet the criteria in recommendation 1.5.15.

1.5.14 In pregnancy or during breastfeeding:

- follow recommendation 1.5.13 **and**

- consider oral vitamin B12 replacement with a dosage of at least 1,000 micrograms a day.

1.5.15 Consider intramuscular vitamin B12 injections instead of oral replacement for suspected or confirmed vitamin B12 deficiency caused by diet if:

- the person has another condition that may deteriorate rapidly and have a major effect on their quality of life (for example, a neurological or haematological condition like ataxia or anaemia)
- there are concerns about adherence to oral treatment, for example, if the person:
  - is older, is or has recently been in hospital and has either multimorbidity or frailty
  - has delirium or cognitive impairment
  - is affected by social issues that may prevent them accessing care, such as homelessness.

In July 2023, this was an off-label use of intramuscular vitamin B12 replacement. See NICE's information on prescribing medicines.

### Unknown causes of vitamin B12 deficiency

1.5.16 In people with a vitamin B12 deficiency where the cause is uncertain or not suspected after further testing or investigations:

- offer vitamin B12 replacement **and**
- consider oral instead of intramuscular vitamin B12 replacement.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on managing vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review E: B12 replacement and self-administration.

## 1.6 Ongoing care and follow-up

1.6.1 At each follow-up appointment:

- ask the person if they are experiencing symptoms or signs of vitamin B12 deficiency **and**
- advise them when to seek medical help (without waiting for any scheduled appointments) if their symptoms have not improved, get worse or return, or they get new symptoms, despite treatment **and**
- if they are taking oral vitamin B12 replacement, check they are taking the correct dosage (if there are any concerns, follow the recommendations on supporting adherence in NICE's guideline on medicines adherence).

1.6.2 Offer an initial follow-up appointment to anyone receiving vitamin B12 replacement:

- at 3 months **or**
- during pregnancy or breastfeeding, at 1 month.

### Follow-up appointments for people taking oral replacement

1.6.3 For people taking oral vitamin B12 replacement, repeat the initial diagnostic test at their first follow-up appointment.

1.6.4 Consider either switching to intramuscular injections or increasing the dosage of oral vitamin B12 replacement, based on the person's preference, if:

- their symptoms have not improved, or they have new symptoms **and**
- the repeated test result suggests they still have a vitamin B12 deficiency.

1.6.5 Continue with oral vitamin B12 replacement if the repeat test suggests the person still has a vitamin B12 deficiency but their symptoms have improved.

1.6.6 If the repeated test suggests the person no longer has a vitamin B12 deficiency and their symptoms have improved, or are no longer present, either:

- continue with oral replacement and agree a date for reassessment if the cause, or suspected cause, of the deficiency has not been addressed (for example, if the person is still taking medicine that could affect vitamin B12 absorption), **or**
- stop treatment if the cause, or suspected cause, has been addressed (for example, if the person is following advice on improving their dietary intake of vitamin B12).

1.6.7 If the repeated test suggests the person no longer has a vitamin B12 deficiency and their symptoms have not improved, or they have new symptoms and they have previously had an MMA test, consider 1 of the following options in agreement with the person:

- switching to intramuscular injections
- increasing the dosage of oral vitamin B12 replacement
- exploring the possibility of alternative diagnoses.

**Further testing with MMA**

1.6.8 Consider an MMA test if a repeat of the initial diagnostic test suggests the person may no longer have a vitamin B12 deficiency but:

- their symptoms have not improved, or they have new symptoms, **and**
- they have not had a previous MMA test.

1.6.9 If the MMA test suggests a vitamin B12 deficiency, consider either:

- switching to intramuscular injections **or**
- increasing the dosage of oral vitamin B12 replacement.

In July 2023, this was an off-label use of intramuscular vitamin B12 replacement. See NICE's information on prescribing medicines

1.6.10 If the MMA test suggests the person no longer has a vitamin B12 deficiency but they still have symptoms, think about alternative diagnoses.

### Follow-up appointments for people receiving intramuscular replacement

1.6.11 Do not repeat the initial diagnostic test in people who are having intramuscular vitamin B12 replacement.

1.6.12 If the symptoms of the person having intramuscular replacement have not improved or they have new symptoms of vitamin B12 deficiency:

- ensure the frequency and dose of vitamin B12 injections are optimised **and**
- agree a date for reassessment of the person's symptoms.

1.6.13 If a person needs lifelong vitamin B12 replacement because they have, or are suspected of having, an irreversible cause of vitamin B12 deficiency but their symptoms have improved, or are no longer present:

- continue with intramuscular injections **and**
- consider an annual follow-up.

1.6.14 If the cause, or suspected cause, of a person's vitamin B12 deficiency has not been addressed but is reversible, and their symptoms have improved, or are no longer present:

- continue with intramuscular injections **and**
- agree a date for their next follow-up.

1.6.15 If the cause, or suspected cause, of vitamin B12 deficiency has been resolved and the person's symptoms have improved, or are no longer present:

- think about stopping or reducing the frequency of the intramuscular injections **and**
- advise them to come back if their symptoms reappear or get worse, or they get new symptoms.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on ongoing care and follow-up.

Full details of the evidence and the committee's discussion are in evidence review F: follow-up.

## 1.7 Monitoring for gastric cancer in people with autoimmune gastritis

1.7.1 At follow-up, take into account that people who have autoimmune gastritis:

- are at higher risk of developing gastric neuroendocrine tumours **and**
- may also be at higher risk of developing gastric adenocarcinoma.

1.7.2 If the person has autoimmune gastritis and new upper gastrointestinal symptoms (for example, dyspepsia, nausea or vomiting):

- consider referral for a gastrointestinal endoscopy **and**
- follow the recommendations on upper gastrointestinal tract cancers in NICE's guideline on suspected cancer.

For a short explanation of why the committee these recommendations and how they might affect practice, see the rationale and impact section on monitoring for gastric cancer in people with autoimmune gastritis.

Full details of the evidence and the committee's discussion are in evidence review G: monitoring for gastric cancer.

# Terms used in this guideline

This section defines terms that have been used in a particular way for this guideline.

### Irreversible cause

A cause of vitamin B12 deficiency that is permanent, even if the deficiency itself can be treated with vitamin B12 replacement. Examples of irreversible causes include

autoimmune gastritis and some types of gastrointestinal surgery, such as major gastric resection, terminal ileal resection and many bariatric operations.

### Reversible cause

A cause of vitamin B12 deficiency that can be reversed, sometimes without the need for vitamin B12 replacement. Examples of reversible causes include insufficient dietary intake of vitamin B12, and factors that affect absorption such as coeliac disease, some medicines and recreational nitrous oxide use.

### Vitamin B12 replacement

Vitamin B12 replacement is where a deficiency is treated with prescribed doses of the vitamin, either as tablets or intramuscular injections, to increase the concentrations in the body.

### Over-the-counter supplements

Vitamin B12 or multivitamin tablets that contain vitamin B12, obtained without a prescription.

## Recommendations for research

The guideline committee has made the following recommendations for research.

### Key recommendations for research

#### 1 Vitamin B12 replacement

What is the clinical and cost effectiveness of vitamin B12 replacement for vitamin B12 deficiency, including the dose, frequency and route of administration?

For a short explanation of why the committee made this recommendation for research, see the rationale section on managing vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review E: B12 replacement and self-administration.

## 2 Diagnosing vitamin B12 deficiency

What are the long-term outcomes for people with suspected vitamin B12 deficiency when comparing testing of total serum B12 (serum cobalamin), active B12 (serum holotranscobalamin), methylmalonic acid (MMA) or homocysteine?

For a short explanation of why the committee made this recommendation for research, see the rationale section on diagnosing vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review C: diagnosis.

## 3 Self-administration

What is the clinical and cost effectiveness of self-administration of parenteral vitamin B12 replacement for deficiency compared with administration by a healthcare professional?

For a short explanation of why the committee made this recommendation for research, see the rationale section on managing vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review E: B12 replacement and self-administration.

## 4 Identifying the cause of vitamin B12 deficiency

What is the clinical and cost effectiveness of pepsinogen, gastrin, parietal cell antibodies and CobaSorb in identifying the cause of vitamin B12 deficiency in people with negative anti-intrinsic factor antibody test results?

For a short explanation of why the committee made this recommendation for research, see the rationale section on identifying the cause of vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review D: identifying cause.

## 5 Follow-up

What should be included in a follow-up review for people with vitamin B12 deficiency, including people with autoimmune gastritis?

For a short explanation of why the committee made this recommendation for research, see the rationale section on ongoing care and follow-up.

Full details of the evidence and the committee's discussion are in evidence review F: follow-up.

# Other recommendations for research

## Risk factors – medicines

Which medicines increase the risk of vitamin B12 deficiency?

For a short explanation of why the committee made this recommendation for research, see the rationale section on recognising vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review B: risk factors and signs and symptoms.

## Risk factors – diet

Which dietary factors increase the risk of vitamin B12 deficiency?

For a short explanation of why the committee made this recommendation for research, see the rationale section on recognising vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review B: risk factors and signs and symptoms.

## Identifying the cause of vitamin B12 deficiency

What is the clinical and cost effectiveness of reflex anti-intrinsic factor antibody testing versus clinician-requested anti-intrinsic factor antibody testing?

For a short explanation of why the committee made this recommendation for research, see the rationale section on identifying the cause of vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review D: identifying cause.

### Monitoring for gastric cancer

What monitoring should be offered to people with autoimmune gastritis to identify gastric cancer?

For a short explanation of why the committee made this recommendation for research, see the rationale section on monitoring for gastric cancer in people with autoimmune gastritis.

Full details of the evidence and the committee's discussion are in evidence review G: monitoring for gastric cancer.

## Rationale and impact

These sections briefly explain why the committee made the recommendations and how they might affect practice.

### Information and support

Recommendations 1.1.1 to 1.1.4

#### Why the committee made the recommendations

The committee agreed it was important to give people information about vitamin B12 deficiency that is tailored to their individual circumstances, including the condition's various symptoms and causes, and what they can expect from investigations and treatment. They also highlighted difficulties in diagnosing vitamin B12 deficiency because its symptoms are also linked to many other conditions. Based on their experience and expertise, the committee also agreed that the limitations of diagnostic tests should be explained to people with suspected vitamin B12 deficiency. In addition, they highlighted situations where it could be difficult to

interpret the test results, such as results that are indeterminate or are affected by the use of over-the-counter supplements. Having these discussions would mean people know what to expect from testing and could prevent any distress or concern if their results are unclear.

Some causes of vitamin B12 deficiency are irreversible and therefore treatment is needed for life. The committee also wanted to reassure people that their vitamin B12 replacement will not be stopped in the future. They also agreed people starting treatment should be told that the dosage and form of vitamin B12 replacement could be adjusted if their symptoms are not resolved or do not improve.

Based on the advice of an expert witness, the committee made a recommendation to address any concerns about the use of nitrous oxide in labour.

### How the recommendations might affect practice

The recommendations reflect current practice and are therefore unlikely to have a big resource impact.

Return to recommendations

## Recognising vitamin B12 deficiency

Recommendations 1.2.1 to 1.2.7

### Why the committee made the recommendations

#### When to test

In the absence of evidence, the committee agreed that vitamin B12 deficiency should be suspected in anyone presenting with at least 1 risk factor and at least 1 symptom or sign. Risk factors, symptoms and signs are not always a clear indication of a vitamin B12 deficiency, but having at least 1 risk factor and 1 symptom or sign increases its likelihood.

The committee agreed that some people who have symptoms and signs but no risk factors may still need a test because they could have a vitamin B12 deficiency and may also be unaware of any risk factors they have. However, it is important to use clinical judgement in deciding when to test when no risk factors are present because

the symptoms and signs of vitamin B12 deficiency are shared by many other conditions. The committee also made a recommendation to help ensure vitamin B12 deficiency is not missed in people who do not have anaemia or macrocytosis, as there is a common misconception that you cannot have a deficiency without either**,** or both**,** of these signs being present.

### Symptoms and signs

The committee agreed that the symptoms and signs associated with vitamin B12 deficiency vary and can also be indicative of other conditions, such as unexplained fatigue. Therefore, it can be difficult to diagnose vitamin B12 deficiency based on symptoms or signs alone. In the absence of evidence and based on their experience and expertise, the committee agreed to a list of symptoms and signs commonly associated with vitamin B12 deficiency, to help prompt suspicion of the condition. This will in turn help ensure deficiency is caught early, preventing any further deterioration in people with the condition.

Based on expert witness advice, the committee agreed that the same symptoms, signs and risk factors would apply in pregnancy and during breastfeeding. However, they also agreed that a poor response to iron treatment is also a sign of vitamin B12 deficiency during pregnancy or breastfeeding so included this in the list of symptoms and signs.

### Risk factors

Using their experience and expertise, the committee agreed to include age as a risk factor for vitamin B12 deficiency. This is because the ageing process causes physiological changes in the gastrointestinal system that can affect dietary intake of vitamin B12, as well as causing malabsorption. Older people are also at higher risk of developing health problems such as cognitive impairment and dementia, which can impact their diet and eating habits.

Anyone who does not eat enough food rich in the vitamin is at risk of developing deficiency. Therefore, based on their experience and expertise, the committee agreed that people who follow a diet that excludes, or is low in, animal-source foods could be at risk of deficiency. However, they acknowledged that people who do not eat, or limit their intake of, animal-sourced foods, can still have a balanced diet and

many take advantage of an increased range of vegetarian and vegan foods, fortified with vitamin B12, that are now available. The committee also made a recommendation for further research into dietary risk factors.

Some conditions and treatments affecting the gastric body (such as coeliac disease, and pelvic and abdominal radiotherapy) can prevent the body from processing vitamin B12 properly. The presence of other autoimmune conditions, which often occur together because of an underlying genetic predisposition, increases the risk of vitamin B12 deficiency because of their association with autoimmune gastritis.

Surgery can also cause vitamin B12 deficiency. Evidence suggests that terminal ileal resection is a risk factor. Based on their experience and expertise, the committee agreed this could be extended to major gastric resections such as total gastrectomy and many bariatric operations.

Some medicines have been linked to vitamin B12 deficiency. Evidence suggested that the use of metformin can lead to a decrease in vitamin B12 concentrations. The use of proton pump inhibitors or $H_2$-receptor antagonists were also found by the evidence to be risk factors. Based on their expertise, the committee agreed that the use of some anti-seizure medicines or colchicine could also be risk factors. They noted there was a lack of evidence on some medicines that may be linked to vitamin B12 deficiency and made a research recommendation in this area.

There is a lack of evidence on how recreational nitrous oxide use affects vitamin deficiency because it is difficult to undertake prospective studies in this area. However, nitrous oxide is known to inactivate vitamin B12 in the body. The committee also acknowledged that recreational use of nitrous oxide is a significant public health issue. In light of this, and based on their experience and expertise, they highlighted recreational nitrous oxide use as a potential risk factor but agreed that more research into the effects of the substance, particularly if it is used regularly or in large amounts, is needed.

The committee also highlighted that people need vitamin B12 replacement after some operations affecting the gastric body. This is usually planned for at the time of surgery. However, there is a risk that some people may not continue with, or have

problems accessing, treatment (for example, if they lived abroad when they had the surgery).

### How the recommendations might affect practice

The symptoms, signs and risk factors included in the recommendations are widely regarded as indications of vitamin B12 deficiency. However, this guideline could lead to a greater awareness of the condition. This may have a potential resource impact as it could lead to more testing and treatment.

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## Diagnosing vitamin B12 deficiency

Recommendations 1.3.1 to 1.3.15

### Why the committee made the recommendations

#### Initial tests

In the absence of high-quality evidence, the committee agreed that either total B12 (serum cobalamin) or active B12 (serum holotranscobalamin) should be the initial diagnostic test for most people. The committee noted that, in their experience, active B12 is a more accurate test than total B12. This is because it measures the form of B12 that is taken up and used by the body, whereas total B12 measures both active and inactive forms. The active B12 test is also significantly more costly. Recommending it over total B12 would therefore lead to a notable change in practice and would be difficult to justify without evidence of cost effectiveness. However, the committee acknowledged that active B12 is a more reliable test during pregnancy and breastfeeding, when total B12 concentrations in the body fall even when there is no deficiency, so they recommended active B12 as the initial test for this group.

Total and active B12 are not suitable tests for people who misuse nitrous oxide because the substance inactivates the B12 molecule, so the person's active or total B12 concentrations would appear to be normal even when they have a deficiency. The committee acknowledged that in this group of people, both homocysteine and methylmalonic acid (MMA) tests are used in current practice to diagnose vitamin B12 deficiency. However, based on their experience, the committee agreed homocysteine

was more reliable because elevated homocysteine in the body is seen before a rise in MMA. People may also need to be given a homocysteine test in hospital if it is not available in primary care, or there are concerns around timing or quality that may mean the test is unreliable.

People with symptoms or signs of vitamin B12 deficiency linked to severe megaloblastic anaemia or sub-acute combined degeneration of the spinal cord need immediate treatment to prevent worsening outcomes, so the committee recommended this should start without waiting for any test results to come back.

The committee emphasised the need to take blood samples from people before they start vitamin B12 replacement treatment, because this could affect their test results. They also highlighted the need to ask people which vitamin B12 supplements they are taking (if any) and at what dosage, because higher doses can elevate vitamin B12 concentrations in the blood and affect test results.

**Factors that can affect initial test results**

The committee were aware that some test results need to be interpreted with caution. These include the results of people who are already taking some form of vitamin B12 supplement, because this could raise the concentrations of the vitamin in the body and therefore mask deficiency. Test results may also be affected by hormonal changes in the body caused by pregnancy, breastfeeding or contraceptive pills.

**Thresholds for initial test results**

In the absence of evidence, the committee used their experience and expertise to define clear thresholds for test results. This will help healthcare professionals decide when to diagnose deficiency and what to do if results are indeterminate or suggest deficiency is unlikely. The committee agreed that the cut-offs they specified for test results may increase the risk of false positives. However, they also agreed that most tests are likely to be used in people who are already symptomatic and that treatment with vitamin B12 replacement is not expensive, nor is it thought to be harmful. The committee also noted that, in current practice, treatment would usually be an option for people with test results near the cut-off for diagnosis. Based on expert witness advice the committee also agreed a higher threshold for diagnosing deficiency during

pregnancy and breastfeeding. This is to ensure any potential deficiency is treated and to protect the health of the baby. There are no generally accepted reference ranges for homocysteine testing therefore the committee agreed that clinical judgement would need to be used when interpreting the test results.

The committee agreed a follow-up MMA test could be an option for people who have an indeterminate result and symptoms of deficiency, because this could potentially lead to an earlier diagnosis if they do have deficiency. They also identified groups of people who should receive treatment without waiting for an MMA test because a delay could adversely affect their quality of life. The economic analyses suggested that, in some cases, this approach could also be more cost effective than testing MMA and then offering treatment. However, an MMA test may still be the best indicator of a deficiency and may be helpful in deciding whether the person needs vitamin B12 replacement in the long term.

Recent evidence from large cohort studies based on samples that are representative of the UK population suggests that people from a Black family background may have a higher reference range for serum concentrations of vitamin B12 in their blood than people from White and Asian family backgrounds. This means people from a Black family background may need treatment even if blood test results show they are not vitamin B12 deficient, and this will need to be taken into account when interpreting test results together with symptoms, signs and risk factors. The committee recommended that treatment should be considered in this group when the test result is indeterminate.

The committee looked at options for people with indeterminate test results who did not have symptoms or signs, such as those who are not suspected of having vitamin B12 deficiency but whose vitamin B12 concentrations were tested as part of routine blood investigations (for example, during a preoperative assessment or general health check). They decided that, for this population, the initial test could be repeated at 6 months to check the person has not developed a deficiency. However, they also agreed that people should come back sooner if symptoms or signs of vitamin B12 deficiency develop.

The committee agreed that people who had a test suggesting deficiency was unlikely but still have symptoms or signs 3 to 6 months on may need a repeat of the test in case the original result was a false negative and they may need treatment.

The committee made a recommendation for further research into which diagnostic testing strategies are best.

### How the recommendations might affect practice

It is unlikely that initial testing using total or active B12 will greatly increase as this is current practice. If more centres decide to use active B12 there will be an increased cost to the NHS because the test is significantly more expensive than a total B12 test. However, this could be offset because, in the committee's view, active B12 is a more accurate test. Currently, MMA testing is not used routinely in primary care for diagnosing vitamin B12 deficiency. The recommendations will lead to a greater awareness of the MMA test and are likely to increase its use as a follow-up test. This will have a resource impact depending on uptake. However, increased use of MMA testing is also likely to lead to faster diagnosis and treatment, while also reducing the number of referrals to secondary care and unnecessary investigations.

The recommendation to only use homocysteine as the initial test for people with nitrous oxide-induced deficiency may reduce the use of MMA testing in this population. This could be cost saving compared to routine practice because people would get their diagnosis and treatment earlier, preventing any further deterioration in their condition.

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## Identifying the cause of vitamin B12 deficiency

Recommendations 1.4.1 to 1.4.4

### Why the committee made the recommendations

The committee agreed it was important to test people with an unknown cause of vitamin B12 deficiency for autoimmune gastritis, because this is an irreversible condition that needs lifelong treatment. The evidence found the anti-intrinsic factor antibody test to be the best initial option for diagnosing autoimmune gastritis.

However, testing everyone with suspected autoimmune gastritis would be very expensive and would not lead to any change in the treatment the person would receive. Therefore, the committee agreed the test was not necessary for people who have already had it (because the result would be the same) or had undergone a gastric operation or some forms of bariatric surgery (because this would be the likely cause of deficiency).

The committee agreed that it was important to test anyone who has suspected autoimmune gastritis during pregnancy or during breastfeeding to ensure their health and that of their baby. For this reason, they also agreed that intramuscular treatment should be started without waiting for test results.

The evidence also showed that, while a positive anti-intrinsic factor antibody test strongly suggests autoimmune gastritis, a negative test is less reliable so cannot be used to rule out the condition. Therefore, some people may need further investigations. Based on their experience and expertise, the committee agreed to a list of some options for further investigations but there was insufficient evidence to recommend 1 over the other. The choice would also depend on the availability of the investigation and whether there were suitably trained and skilled healthcare staff available to carry it out. Therefore, the committee agreed to make a recommendation for further research to determine the most effective investigations for people with negative anti-intrinsic factor antibody test results.

It was unclear from the evidence whether it is more clinically and cost effective to do reflex testing for anti-intrinsic factor antibodies when a low vitamin B12 concentration is detected, or for clinicians to request testing based on their own clinical judgement. Therefore, the committee made a research recommendation in this area.

### How the recommendations might affect practice

It is usual practice to request an anti-intrinsic factor antibody test when autoimmune gastritis is suspected, therefore the recommendations are unlikely to have a big impact.

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# Managing vitamin B12 deficiency

Recommendations 1.5.1 to 1.5.16

## Why the committee made the recommendations

Evidence for the effectiveness of vitamin B12 replacement was mainly gathered from studies that were based on blood test results and made little reference to quality of life or other patient-reported outcomes, such as an improvement in symptoms. While increasing vitamin B12 concentrations is the aim of treatment, based on their experience and expertise, the committee agreed the management of deficiency should also be based on both the cause of deficiency and factors such as symptoms. They also agreed there was a need for further research into the optimal treatment strategies for different causes of deficiency, particularly focusing on patient-reported outcomes.

Based on their experience and expertise, the committee recommended that all people with vitamin B12 deficiency should be given an estimated timeframe for symptom improvement so they will seek help if their symptoms are not improving as expected.

Based on expert witness advice, the committee agreed that treatment with vitamin B12 replacement should continue if it was started before pregnancy or breastfeeding. This is because there is no harm associated with vitamin B12 replacement and stopping treatment may lead to a return of, or worsening, symptoms and potentially cause harm.

### Deficiency caused by malabsorption

The committee agreed that anyone with confirmed vitamin B12 deficiency caused by autoimmune gastritis should receive lifelong intramuscular vitamin B12 replacement. This is because their bodies cannot adequately absorb vitamin B12 through the gastrointestinal tract, often making oral replacement ineffective. Intramuscular injections are also cheaper than oral replacement if used for 6 months or more. Autoimmune gastritis is often difficult to diagnose, so the committee also agreed that people who are likely to have the condition should have the same treatment as those with a diagnosis. This could prevent the effects of vitamin B12 deficiency becoming permanent.

The committee agreed that those who have undergone an operation that has permanently prevented the body from absorbing vitamin B12 properly (such as a major gastric resection, terminal ileal resection or certain types of bariatric surgery) need lifelong vitamin B12 replacement. As well as being more cost effective than oral replacement when used for 6 months or more, intramuscular vitamin B12 replacement could also be the better option for these groups of people because it can be difficult to judge how much of an oral dose will be absorbed by the body and the injections will help ensure the person is getting enough of the vitamin. However, there was no evidence to suggest that oral replacement was ineffective in these groups, so the committee agreed to include it as an alternative treatment option.

People who have vitamin B12 deficiency caused by malabsorption for other reasons (such as coeliac disease) may not need lifelong treatment. In these groups of people, the body may have some ability to absorb vitamin B12, provided the malabsorption is managed, and the deficiency could potentially be reversed in the long-term (for example, in coeliac disease by following a gluten-free diet). In the absence of evidence favouring 1 treatment over the other, the committee agreed, based on their experience and expertise, to recommend that these groups of people could receive either intramuscular or oral vitamin B12 replacement, depending on individual preference.

**Medicine-induced deficiency**

There was no evidence to suggest either oral or intramuscular vitamin B12 replacement was better for medicine-induced deficiency. So, based on their experience and expertise, the committee agreed that people with medicine-induced deficiency should be offered either option depending on the person’s preference. Vitamin B12 replacement should also continue for as long as they remain on the medicine, because the deficiency is otherwise unlikely to be resolved. If possible, medicine that can cause vitamin B12 deficiency should be stopped or changed. The committee agreed that if the medicine is stopped, or the person no longer has symptoms of vitamin B12 deficiency, the need for vitamin B12 replacement should be reviewed. This is because the cause of deficiency would have been removed.

### Nitrous oxide-induced deficiency

Nitrous oxide is known to cause vitamin B12 deficiency by inactivating the vitamin, but its longer-term effects are unknown. There was no evidence to suggest either oral or intramuscular vitamin B12 replacement was a better treatment for nitrous oxide-induced deficiency so the committee agreed that either should be offered, based on the person's preference. People should be advised to stop using nitrous oxide recreationally to prevent their deficiency from getting worse. They will also need to continue with vitamin B12 replacement even after they have stopped using nitrous oxide, because it is unclear how long it will take for any deficiency caused by the substance to resolve.

### Dietary deficiency

Deficiency caused by a diet lacking in vitamin B12 is potentially reversible. Based on their experience and expertise, the committee agreed it was important for healthcare professionals to talk to people who have a suspected dietary deficiency about what they eat, as well as their symptoms, signs and risk factors, to establish if this is the cause of deficiency. They also noted that diet can be assumed to be a cause of deficiency in people who may have it for other reasons, including in those who are vegetarian or vegan but still make sure they get enough of the vitamin through their diet. This misconception could potentially lead to under-investigation of potential causes of deficiency, such as autoimmune gastritis, which can have serious long-term implications if left undiagnosed.

The committee also wanted to raise awareness of the wide variation in forms of over-the-counter supplements. While some can effectively treat deficiency, others do not contain enough or the right type of the vitamin. Therefore, the committee agreed to list the types of vitamin B12 people should look out for should they wish to buy supplements.

Based on their experience and expertise, the committee agreed deficiency could be reversed in some people if they changed their diet, without the need for treatment. However, there was a lack of evidence in this area, so they also recommended oral vitamin replacement for some people with a dietary deficiency.

Based on expert witness advice, the committee also agreed that oral vitamin B12 replacement prescribed during pregnancy or breastfeeding should be given at a dosage of at least 1,000 micrograms a day. This is because the body can need more vitamin B12 in pregnancy and during breastfeeding, so setting a minimum dose will ensure that enough vitamin is being absorbed. This should help ensure the health of anyone who is pregnant or breastfeeding, and of their child.

Intramuscular vitamin B12 replacement could be the best option for people in whom treatment needs to work quickly because they are at risk of rapid deterioration that could significantly affect their quality of life. Injections could also be a better option if there are concerns about adherence to oral replacement. This could include concerns about older people who are in or have recently been in hospital, and also have complex comorbidity, or have frailty linked to undernutrition, dementia or decompensation. This group is likely to be prescribed a few different medicines to take on a daily basis. The committee recommended intramuscular vitamin B12 replacement is considered because having intramuscular injections at 2 to 3-month intervals would mean 1 less medicine to take a day and address any concerns with adherence to taking tablets. Intramuscular injections are also likely to be more effective in managing the vitamin B12 deficiency. Adherence may also be an issue for some people who are not in hospital but who may find it difficult, or may be unable, to collect, store or take their medicine.

**Unknown causes of vitamin B12 deficiency**

In the absence of evidence, the committee used their experience and expertise to recommend vitamin B12 replacement to anyone presenting with a deficiency without a known or suspected cause because this should correct the deficiency. They also agreed that oral vitamin B12 replacement should be considered instead of intramuscular injections. This is because any necessary investigations will have been completed and vitamin B12 deficiency is unlikely to be caused by malabsorption in these groups of people.

**Self-administration of vitamin B12 replacement**

No evidence comparing self-administered intramuscular or subcutaneous vitamin B12 injections with those administered by healthcare professionals was identified.

Patient preference, the precedent for self-administration of vitamin B12 replacement set during the COVID-19 pandemic, and potential cost savings for the NHS were all considered. However, the committee decided to make a recommendation for further research to inform future guidance because there were no data on the effectiveness or safety of self-administration.

### How the recommendations might affect practice

The recommendations for treating deficiency of any cause other than diet reflect current practice and are unlikely to have a resource impact.

Most of the recommendations for managing dietary deficiency also reflect current practice. However, the use of intramuscular instead of oral replacement when there are concerns about adherence will be a change in practice. This is unlikely to have a significant resource impact if no loading dose is needed because it will always be cost saving compared to oral treatment. If a loading dose is needed, then intramuscular injections will be cost effective if treatment is continued for longer than 6 months.

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## Ongoing care and follow-up

Recommendations 1.6.1 to 1.6.15

### Why the committee made the recommendations

Discussing symptoms and signs at follow-up would give an indication of how well treatment is working. The committee agreed that it is also important to look at changes to symptoms, especially symptoms that are so severe that they impact on daily activities. The committee also emphasised that people receiving treatment should seek medical help if they need it, without waiting for a further follow-up appointment, to ensure the treatment is working properly. With oral vitamin B12 replacement, it is also important to check the person is taking the correct dosage as this can help identify any issues with adherence.

There was no evidence on the most effective ongoing care and follow-up strategies for people with vitamin B12 deficiency, so the committee made recommendations

based on consensus. For most people, a follow-up at 3 months would give enough time to ensure treatment is working. However, anyone who is pregnant or breastfeeding should be followed up sooner to make sure they are getting the treatment they need to protect both their health and that of their baby.

The committee also made a research recommendation into which components of follow-up reviews lead to the best outcomes for people receiving either oral or intramuscular vitamin B12 replacement. In particular, they agreed further research was needed into:

- the measurement of different haematological values
- assessment for dietary intake of vitamin B12
- assessment for the symptoms for vitamin B12 deficiency.

**Follow-up appointments for people taking oral replacement**

In people taking oral replacement, the committee agreed vitamin B12 concentrations should be tested again at the first follow-up appointment. This would allow adequate time for treatment to work and will indicate if the person's body is able to absorb the vitamin. They also agreed that anyone on oral replacement should be reviewed if the repeated test shows they still have a deficiency and they have symptoms that have not improved, because this suggests treatment is not working properly. However, if the person still has a deficiency but their symptoms have improved, then the committee agreed that it is likely that oral treatment is working and it should therefore continue.

A decision about further treatment in people whose symptoms have improved, and whose test results suggest they no longer have a vitamin B12 deficiency depends on whether the underlying cause, or suspected cause, of the deficiency has been addressed. Treatment could be stopped if the cause has been addressed to prevent any further, unnecessary treatment, but otherwise it would need to continue to prevent the deficiency from returning.

If the repeated test suggests the person does not have a deficiency but symptoms have not improved then oral replacement will still need to be reviewed. This is because people on oral treatment may still experience symptoms despite normal test

results. If the person has not previously had an MMA test then, as well as thinking about changing treatment, the possibility of alternative diagnoses may also need to be explored. This is because the symptoms for vitamin B12 deficiency overlap with a number of conditions and the result may indicate that different, or additional, treatment to vitamin B12 replacement is needed.

An MMA test should be considered if the person has not previously had one and their symptoms have not improved, or they have new symptoms. This is because this test may help determine if the person still has a deficiency, whether their treatment should be changed or if their symptoms are caused by another condition.

**Follow-up appointments for people receiving intramuscular replacement**

The committee agreed there was little benefit in repeating the initial diagnostic test to measure serum B12 concentrations in people receiving intramuscular vitamin B12 replacement. This is because the treatment will influence the test and the result will not be an accurate reflection of how well it is working. Therefore, the committee agreed that it was more important to focus on symptoms and signs at follow-up appointments. If the person's symptoms have not improved, or they have new symptoms, then it is likely that the effects of the treatment are wearing off before the next planned injection date. Based on their experience and expertise, the committee agreed that, in this case, increasing the frequency of injections may help improve the person's symptoms.

The form of ongoing care and follow-up also depends on the cause of the deficiency. The committee agreed that those with an irreversible cause would need to continue with intramuscular injections. It is usual practice for people on long-term treatment to have an annual medicines review. Therefore, the committee agreed that this could align with a 1-year follow-up for people with an irreversible cause of vitamin B12 deficiency whose symptoms have improved or they are symptom-free.

People with a cause that is potentially reversible would need to continue with treatment until it has been addressed and their symptoms have improved or are no longer present. If the cause and the symptoms have been addressed, then further treatment is unlikely to be necessary and could be either stopped, or the frequency of the injections could be reduced. However, they should be advised to return if

symptoms reappear, as this may indicate that the deficiency has returned and they may need further treatment.

### How the recommendations might affect practice

The recommendations largely reflect current practice. Usually, people are asked to seek medical help if treatment does not work and people on long-term treatment have an annual follow-up, so the recommendations would not have a big resource impact. Offering everyone a follow-up appointment at 3 months (or 1 month during pregnancy or breastfeeding) will also help ensure the person has the right diagnosis and treatment. This will help prevent unnecessary treatment, which will outweigh any additional costs related to follow-up appointments.

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## Monitoring for gastric cancer in people with autoimmune gastritis

Recommendations 1.7.1 and 1.7.2

### Why the committee made the recommendations

There was no evidence demonstrating the effectiveness of monitoring people with autoimmune gastritis for gastric cancer. However, based on their experience and expertise, the committee agreed it was important to highlight the increased incidence of gastric adenocarcinoma and gastric neuroendocrine tumours in people with autoimmune gastritis. Raising awareness of this may mean people are more likely to report any gastrointestinal symptoms to their healthcare professional. They also stressed that people may need referral for gastrointestinal endoscopy if they have new upper gastrointestinal symptoms (for example, dyspepsia, nausea or vomiting) as these could suggest the presence of cancer.

The committee also made a recommendation for research on monitoring for gastric cancer in people with autoimmune gastritis.

### How the recommendations might affect practice

These recommendations reflect current practice and are unlikely to have a resource impact.

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# Context

Vitamin B12 deficiency is caused by a lack of the vitamin in the diet, problems with absorption from the gastrointestinal tract (for example, because of autoimmune gastritis), or recreational nitrous oxide use (because this substance inactivates vitamin B12 in the body). The condition can lead to a wide range of symptoms and complications, including mental health problems and neurological problems such as cognitive impairment. It is more common in older people and is thought to affect around 5% of people aged between 65 and 74 years and more than 10% of people aged 75 and over.

Vitamin B12 deficiency is usually diagnosed and treated in primary care. A blood test for deficiency is usually done when people present with symptoms like fatigue, which can be common of many conditions, or when there are abnormal findings on other blood tests. Testing is also done when investigating conditions such as anaemia, macrocytosis, and neuropsychiatric or neurodegenerative symptoms or signs.

Treatment for vitamin B12 deficiency depends on the cause but the aim is to replace vitamin B12 and improve the person's symptoms. The most common treatments are intramuscular injections, given by a healthcare professional, or oral vitamin B12 replacement.

This guideline aims to improve the diagnosis and management of vitamin B12 deficiency, including deficiency caused by autoimmune gastritis, reduce complications and improve quality of life for people with suspected and confirmed deficiency.

# Finding more information and committee details

To find NICE guidance on related topics, including guidance in development, see the NICE webpage on blood conditions.

For details of the guideline committee see the committee member list.