Appendix

There are currently no formal consensus screening or treatment guidelines in managing the risk of B12 deficiency in the infants of B12 deficient mothers. This shortfall may be contributing to the results described in this study. The recommendations that follow are not systematic guidelines, but rather intend to provide pragmatic advice to the clinician managing a pregnancy or infancy at risk of B12 deficiency in New Zealand based on the local context described in this study and other recent emerging evidence.

These recommendations specifically target infants at high risk of B12 deficiency; they do not provide comprehensive guidance regarding the investigation and management of B12 deficiency in pregnant women. For systematic guidelines regarding the management of B12 deficiency in adults, refer to the National Institute for Care and Excellence (NICE) guideline *Vitamin B12 deficiency in over 16s: diagnosis and management*.[28]

A) Screening recommendations

Recent evidence suggests that the vast majority of infants at risk of B12 deficiency will experience normal neurodevelopment with no medical consequences, including those who are mild–moderately deficient.[22] However, B12 deficiency that is severe and prolonged can cause irreversible neurological harm to an infant. The goal of these recommendations is to identify these infants with the highest risk for severe deficiency, and to effectively reduce their risk through dietary and pharmacological intervention both before and after birth. Where dietary/supplementation advice is recommended, refer to *B) Nutrition and treatment recommendations*. Allowing for the margin of error of the laboratory assay and the lack of consensus definition for deficiency, thresholds have been rounded up to the nearest 10pmol/L for simplicity.

Pregnancy (see Appendix Figure 1)

1. **Take a medical and dietary history in the first trimester to identify risk factors for deficiency**. See Appendix Table 1 and *Appendix—B) Nutrition and treatment recommendations*.
2. **If a woman has no risk factors, then testing is not recommended**. Most women do not require B12 testing or supplementation in pregnancy.
3. **If a woman has any risk factor for B12 deficiency, provide dietary/supplementation advice and measure serum B12 alongside other routine antenatal screening blood tests at the first booking appointment (ideally in the first trimester)**. Antenatal serum B12 levels trend downwards as gestation progresses due to normal physiological changes in pregnancy; therefore, early antenatal serum B12 levels are a more representative screening test for deficiency in the mother.[1,2]
4. **Recommended management according to antenatal serum B12 level (ideally measured first trimester):**
   A. >400pmol/L: no further testing or treatment is recommended due to the low risk for infant deficiency.[2]
   B. 150–400pmol/L: reiterate diet/supplementation advice. Further testing or treatment has not been shown to improve infant neurodevelopmental outcomes.[22]
   C. 100–149pmol/L: recommend antenatal oral or intramuscular B12 treatment to reduce the infant's risk of deficiency. Reiterate diet/supplementation advice.
   D. <100pmol/L: recommend administration of intramuscular B12 treatment to reduce the infant's risk of deficiency. Reiterate diet/supplementation advice.
5. **If B12 deficiency is appropriately treated antenatally, then follow-up testing of the mother is not required.**
6. **If serum B12 level is <150pmol/L at any gestation, refer to the "Infancy" recommendations to guide management of the infant** (see Appendix Figure 2). Refer to the NICE Guidelines for advice regarding investigation of the underlying cause of B12 deficiency in pregnant adults.[28]

Infancy (see Appendix Figure 2)

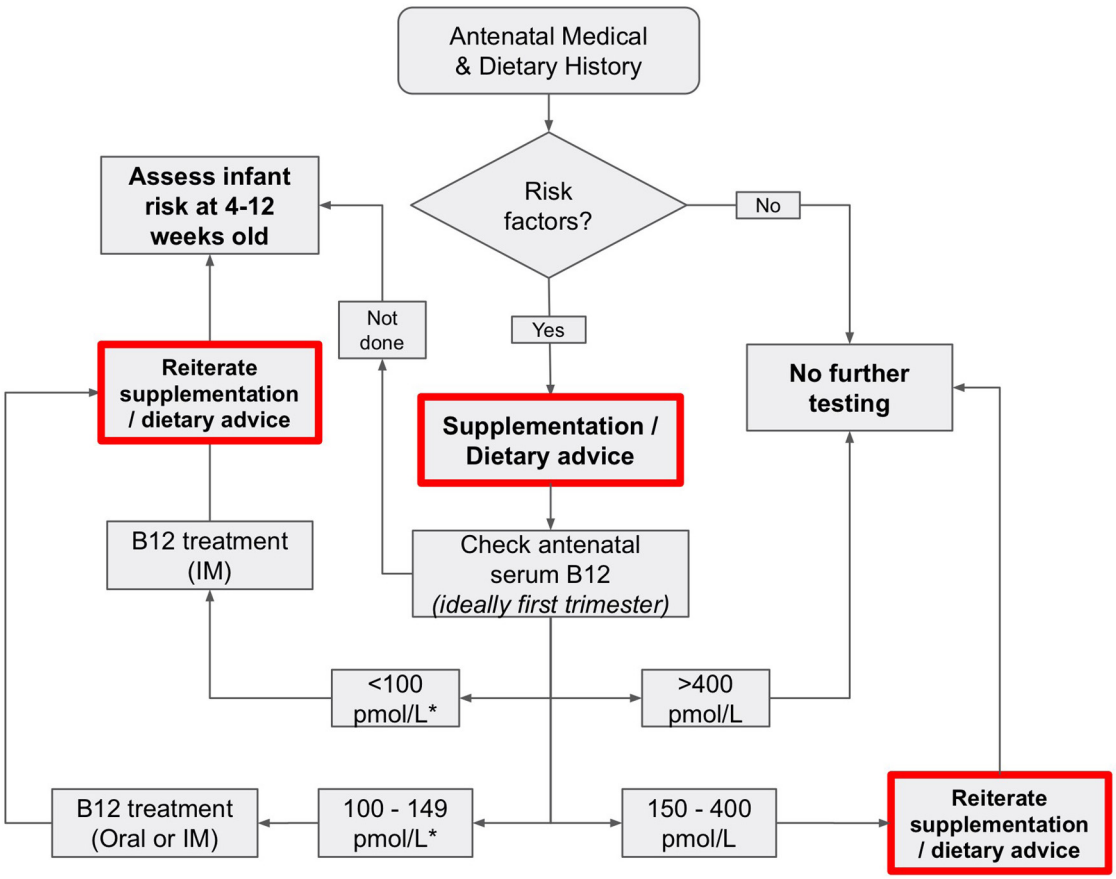
1. **If antenatal serum B12 was <150pmol/L at any gestation, or if any maternal risk factors for deficiency were present but antenatal serum B12 levels were not measured, then the infant is at risk of B12 deficiency.** Provide dietary/supplementation advice. This risk factor must be included in any handover of care from antenatal care to primary care (e.g., general practitioner).
2. **Reassess infant risk between 4–12 weeks old** (e.g., at time of discharge from lead

Appendix Table 1: Maternal risk factors for infant B12 deficiency.[1,8]

Previous antenatal B12 deficiency
Previous child with B12 deficiency
Limited consumption of animal products, particularly red meat (vegetarian/vegan diet, socio-economic factors, eating disorders)*
Gastrointestinal condition causing B12 malabsorption (pernicious anaemia, significant disease or surgery affecting the stomach, ileum or pancreas, inflammatory bowel disease)
Unexplained or macrocytic anaemia
Genetic disorder of B12 metabolism
Chronic use of medications/substances that affect B12 absorption or metabolism (e.g., metformin, proton pump inhibitor, H2-receptor antagonists, excess alcohol)
History of autoimmune disease (e.g., Coeliac, autoimmune thyroiditis, type 1 diabetes)

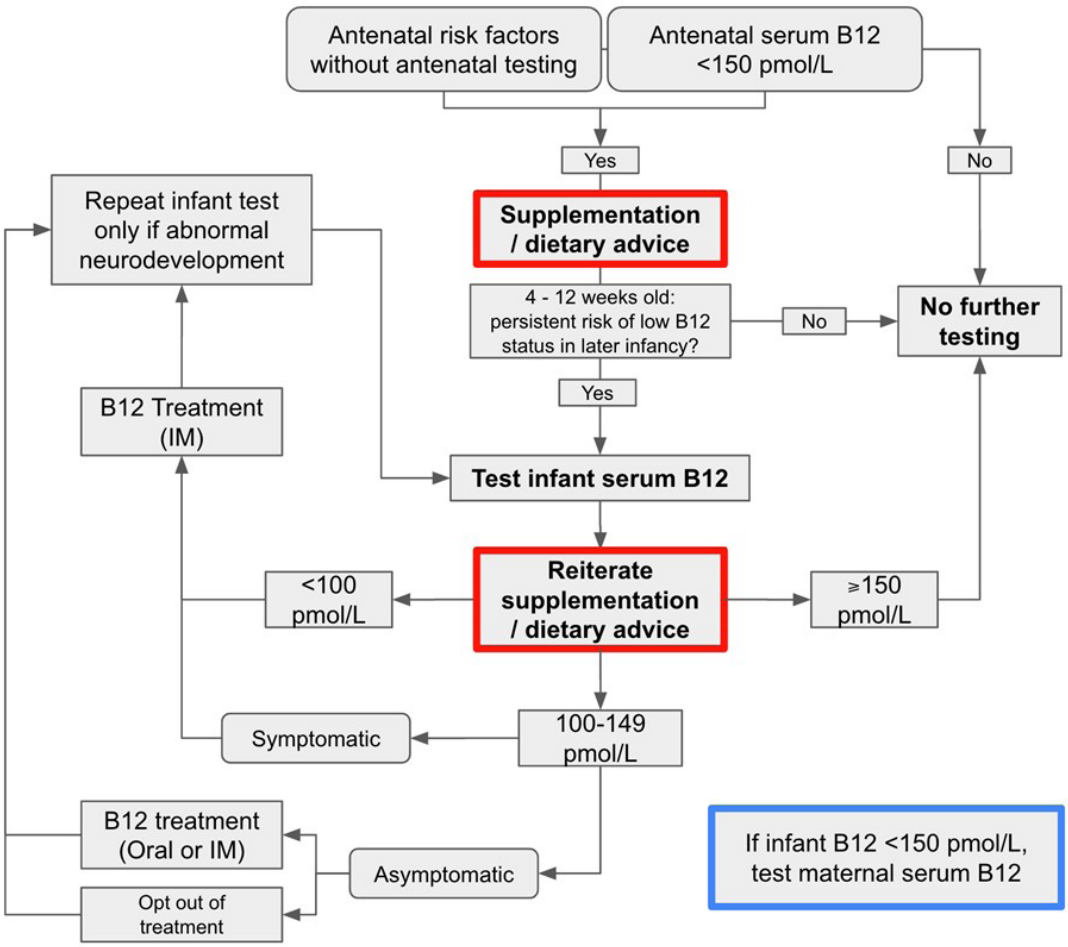
*See Appendix—*B) Nutrition and treatment recommendations*.

Appendix Figure 1: Antenatal recommendations flowchart.



*Refer to NICE guidelines regarding investigation of cause of B12 deficiency.[28]

Appendix Figure 2: Infant recommendations flowchart.



maternity carer [LMC] care, or during the "6-week infant check" in primary care). If a risk reduction strategy has been put in place (e.g., infant/maternal B12 supplementation, plan for prioritised introduction of animal products into diet when the infant starts solids—see *Appendix*), then no further testing is needed. However, if no risk reduction strategy is in place, the infant remains at risk of B12 deficiency; **test serum B12 in these selected infants while reiterating dietary/supplementation advice.**

3. **Recommended management according to infant serum B12 level:**
   A. <100pmol/L: strongly recommend B12 treatment via the intramuscular route.
   B. 100–149pmol/L: if symptomatic, treat as per (A) above. If asymptomatic, provide treatment based on family preference. If they opt out of treatment, monitor the infant clinically for symptoms of B12 deficiency, particularly abnormal neurodevelopment.
   C. ≥150pmol/L: no treatment is required.
4. **Follow-up testing is not required in most infants, regardless of treatment.** The exception is when specific symptoms develop in later infancy suggestive of severe B12 deficiency, particularly abnormal neurodevelopment.
5. **If an infant's serum B12 is <150pmol/L, measure the B12 status of the mother.** If she is also found to be B12 deficient, treat as per NICE guidelines.[28]

B) Nutrition and treatment recommendations

Diet is the most important determinant of a person's B12 status. The consumption of red meat is the main dietary factor correlating to serum B12 concentration in the New Zealand population.[8] When taking an antenatal dietary history,

specifically ask about consumption of animal products, with particular attention in patients of South Asian (defined as people with ancestral origins in the Indian subcontinent including India, Afghanistan, Pakistan, Sri Lanka, Nepal, Bangladesh, Bhutan and the Maldives) and Fijian Indian ethnicities, where reduced animal product consumption is more prevalent due to cultural and religious practices.[8] Other factors causing food restriction (such as socio-economic deprivation or eating disorders) may also limit a person's ability to regularly consume animal products or B12 supplementation.[1]

The antenatal recommended daily intake (RDI) for B12 is 2.6mcg/day (increased from 2.4mcg/day for non-pregnant adults due to placental and foetal demand), and further increases to 2.8mcg/day when breastfeeding.[29] Pregnant women with a diet inclusive of animal products will usually meet this requirement by following the Ministry of Health guidance on *Safe and healthy eating in pregnancy*, consuming at least three servings per day from the following food groups: lean meat, poultry, seafood, eggs, nuts, seeds and legumes, while prioritising the consumption of animal products.[10] If a pregnant woman is vegetarian or vegan, they are recommended to take an oral supplement providing at least the RDI of vitamin B12 due to the variable levels of B12 in fortified food products.[10] There are numerous inexpensive oral vitamin supplements containing B12 that are commercially available in New Zealand, although none are currently subsidised for pregnant women or infants.

In infants with risk factors or a confirmed diagnosis of B12 deficiency, do not delay introducing solids beyond 6 months of age, and consider introduction of solids from 4 months of age if the infant is developmentally ready. Prioritise B12-rich foods such as well-cooked and pureed meat, seafood and egg. B12 supplementation is recommended in children older than 6 months who transition to a diet that restricts animal products, or have a malabsorptive medical condition, or have not introduced solids or fortified milk formula into the diet. Refer to a New Zealand Registered Dietitian for individualised advice.

If treatment doses of B12 are required for either a mother or infant, both oral and parenteral B12 are considered equally effective unless enteral dosing is contraindicated (e.g., pernicious anaemia or other malabsorptive condition).[30] B12 has minimal risk of toxicity even in large doses.[1,30] In severe deficiency, considering the potential for neurodevelopmental impairment, we have advised intramuscular B12 be given in alignment with NICE guidelines as it guarantees adherence, has high bioavailability and is subsidised.[28,30] Refer to the New Zealand Formulary for intramuscular dosing. Alternatively, high dose oral B12 can be given; there is no standard dose, but a several week course of high dose oral B12 at 500–1,000mcg per day can be safely administered in both women and infants.[1,13,28,30]

Measuring follow-up serum B12 levels within 3 months of intramuscular B12 treatment is not useful as these levels are often misleadingly elevated and do not accurately reflect body stores.[28]