EtD 15. What is the recommended vitamin intake by postnatal age? Fat-soluble vitamins (vitamin A, E, D, K), Water soluble vitamins (B vitamins, vitamin C, choline)?

POPULATION:	Preterm infants
INTERVENTION:	Higher vitamin intake
COMPARISON:	No/lower vitamin intake
MAIN OUTCOMES:	**Critical outcomes** Mortality Neurodevelopmental impairment **Important but not critical** Adverse effects (prevention of unnecessary blood tests) Faltering growth/body composition Retinopathy of prematurity Bronchopulmonary dysplasia Fully breastfed or breastmilk feeding at hospital discharge Time to full enteral feeds Duration of initial hospital stay Sepsis: proven or suspected Necrotising enterocolitis Anaemia of prematurity Cost: cost of intervention, cost of neonatal care and life-long cost **Less important for decision making** Time to full sucking feeds
SETTING:	Neonatal care
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	Preterm infants face numerous challenges because they are born with immature metabolic, immune, and organ systems, and often have little to no subcutaneous fat, glycogen, minerals, or vitamin stores. These infants are at heightened risk of malnutrition and suboptimal neurodevelopmental and health outcomes later in life. Adequate nutrition, including essential vitamins, is critical in the neonatal period to support growth, immune function, metabolic processes, and brain maturation. Vitamins are essential micronutrients that cannot be synthesised by the human body in sufficient quantities. They serve diverse roles, such as acting as cofactors in enzymatic reactions, regulating gene expression, and supporting energy metabolism and immune responses. Vitamin deficiencies in preterm infants can result in severe or fatal consequences. However, determining the optimal PN vitamin requirements for preterm infants remains a significant challenge. Current recommendations for both fat-soluble and water-soluble vitamins in preterm infants are based on estimations rather than robust evidence. Some guidelines provide very wide intake ranges for specific vitamins, reflecting

	the lack of conclusive research. These disparities in guidelines may lead to either under- or over-supplementation, potentially impacting health outcomes. Until more high-quality evidence is available, vitamin supplementation practices will continue to rely on estimations and clinical judgment, emphasising the need for close monitoring to ensure that vitamin intake meets but does not exceed requirements.
CONFLICT OF INTERESTS:	The following vitamin systematic review (Bronnert *et al*) co-authors are on the Guideline Development Group: Barbara Cormack, Frank Bloomfield and Luling Lin and on the Guideline Development Group: Barbara Cormack, Luling Lin and Frank Bloomfield and supervised the first author. The following systematic review on Guidelines (Meiliana M, et al) co-authors are on the Guideline Development Group: Barbara Cormack, Tanith Alexander, Luling Lin and Frank Bloomfield and supervised the first author.

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Evidence from a systematic review (Bronnert *et al*) [1] and a systematic review (Meiliana *et al*) which summarised guideline recommendations [2]. **ESPGHAN recommendations for vitamins [3,4]:** Vitamin A ESPGHAN (enteral) 2022 All preterm: 1,333-3,333 IU.Kg-1.day-1 (Strong) ESPGHAN (parenteral) 2018 All preterm: 700-1,500 IU.Kg-1.day-1 (Weak) Vitamin E ESPGHAN (enteral) 2022 All preterm: 2.2-11 IU.Kg-1.day-1 (Strong) ESPGHAN (parenteral) 2018 All preterm: 2.8-3.5 IU.Kg-1.day-1, ≤11 mg/day (Strong) Vitamin D ESPGHAN (enteral) 2022 All preterm: 400-700 IU.day-1 (Strong) ESPGHAN (parenteral) 2018 All preterm: 200-1,000 IU.day-1 (Strong) Vitamin K ESPGHAN (enteral) 2022 All preterm: 4.4-28 µg.Kg-1.day-1 (Strong) ESPGHAN (parenteral) 2018 All preterm: 10 µg.Kg-1.day-1 (Strong) Vitamin C ESPGHAN (enteral) 2022 All preterm: 17-43 mg.Kg-1.day-1 (Weak) ESPGHAN (parenteral) 2018 All preterm: 15-25 mg.Kg-1.day-1 (Strong) Vitamin B1	**Population information for included evidence** Bronnert systematic review was on very low birthweight and very preterm infants

	ESPGHAN (enteral) 2022 All preterm: 140-290 µg.Kg-1.day-1 (Weak) ESPGHAN (parenteral) 2018 All preterm: 350-500 µg.Kg-1.day-1 (Weak) Vitamin B2 ESPGHAN (enteral) 2022 All preterm: 200-430 µg.Kg-1.day-1 (Weak) ESPGHAN (parenteral) 2018 All preterm: 150-200 µg.Kg-1.day-1 (Weak) Vitamin B3 ESPGHAN (enteral) 2022 All preterm: 1.1-5.7 mg.Kg-1.day-1 (Weak) ESPGHAN (parenteral) 2018 All preterm: 4.0-6.8 mg.Kg-1.day-1 (Weak) Vitamin B5 ESPGHAN (enteral) 2022 All preterm: 0.6-2.2 mg.Kg-1.day-1 (Weak) ESPGHAN (parenteral) 2018 All preterm: 2.5 mg.Kg-1.day-1 (Weak) Vitamin B6 ESPGHAN (enteral) 2022 All preterm: 70-290 µg.Kg-1.day-1 (Weak) ESPGHAN (parenteral) 2018 All preterm: 150-200 µg.Kg-1.day-1 (Weak) Vitamin B7 ESPGHAN (enteral) 2022 All preterm: 3.5-15 µg.Kg-1.day-1 (Weak) ESPGHAN (parenteral) 2018 All preterm: 5.0-8.0 µg.Kg-1.day-1 (Weak) Vitamin B9 ESPGHAN (enteral) 2022 All preterm: 23-100 µg.Kg-1.day-1 (Weak) ESPGHAN (parenteral) 2018 All preterm: 56 µg.Kg-1.day-1 (Strong) Vitamin B12 ESPGHAN (enteral) 2022 All preterm: 0.1-0.6 µg.Kg-1.day-1 (Weak) ESPGHAN (parenteral) 2018 All preterm: 0.3 µg.Kg-1.day-1 (Weak) Choline - ESPGHAN (enteral) 2022 All preterm: 8-55 mg.Kg-1.day-1 (Weak) **Vitamin C** **No faltering growth/body composition**: RCT: No significant effect in weight with increased dose (MD 0.2 g/day higher; 4.42 lower to 4.82 higher) [Important]. **Retinopathy of prematurity**: RCT: No significant reduction in retinopathy of prematurity with higher dose (4 fewer per 1,000; 166 fewer to 279 more) [Important]. **Bronchopulmonary dysplasia/chronic lung disease**: RCT: Very large reduction in bronchopulmonary	

	dysplasia with higher dose (176 fewer per 1,000; 270 fewer to 30 fewer) [Important]. **Sepsis**: RCT: No significant reduction in culture proven sepsis with higher dose (156 fewer per 1,000; 316 fewer to 188 more) [Important]. **Vitamin E** **Mortality**: RCT: No significant effect on mortality with higher dose (4 fewer per 1,000; 35 fewer to 35 more) [Critical]. **Retinopathy of prematurity**: RCT: No significant reduction in retinopathy of prematurity with higher dose (49 fewer per 1,000; 131 fewer to 53 more) [Important]. **Bronchopulmonary dysplasia:** RCT: No significant reduction in bronchopulmonary dysplasia with higher dose (16 fewer per 1,000; 55 fewer to 31 more) [Important]. **Anaemia of prematurity**: RCT: No significant effect in the number of transfusions per infant (MD 0.2 transfusions lower; 1.18 lower to 0.78 higher) [Important]. **Vitamin D** **Neurodevelopmental impairment**: RCT: No significant reduction in neurodevelopmental impairment (120 fewer per 1,000; 270 fewer to 135 more); cognitive impairment (63 fewer per 1,000; 216 fewer to 228 more) or language impairment (129 fewer per 1,000; 302 fewer to 129 more) at 22-26 months [Critical]. **No faltering growth/body composition**: RCT: No significant increase in weight with increased dose (MD 2.0 g/day higher; 2.38 lower to 6.38 higher) [Important]. **Retinopathy of prematurity**: RCT: No significant reduction in retinopathy of prematurity with higher dose (105 fewer per 1,000; 265 fewer to 165 more) [Important]. **Bronchopulmonary dysplasia**: RCT: Very large reduction in bronchopulmonary dysplasia with higher dose (169 fewer per 1,000; 237 fewer to 68 fewer)[Important]. **Sepsis**: RCT: No significant reduction in culture proven sepsis with higher dose (156 fewer per 1,000; 316 fewer to 188 more) [Important]. **Vitamin A** **Mortality**: RCT: No significant effect in mortality for larger dose (3 fewer per 1,000; 23 fewer to 21 more) [Critical]. **Neurodevelopmental impairment**: RCT: No significant reduction in neurodevelopmental impairment (53 fewer per 1,000; 125 fewer to 38 more); cognitive impairment (66 fewer per 1,000; 132 fewer to 16 more); motor impairment (50 fewer per 1,000; 110 fewer to 30 more) and cerebral palsy (31 fewer per 1,000; 77 fewer to 36 more) [Critical]. **Retinopathy of prematurity**: RCT: Very large reduction of retinopathy of prematurity with larger dose (98 fewer per 1,000; 166 fewer to 9 fewer) [Important]. **Bronchopulmonary dysplasia**: RCT: No significant reduction in bronchopulmonary dysplasia with larger dose (65 fewer per 1,000; 130 fewer to 6 more) [Important]. **Sepsis**: RCT: Very large reduction in culture proven sepsis (28 fewer per 1,000; 54 fewer to 0 fewer) and	

	culture proven or suspected sepsis with larger dose (30 fewer per 1,000; 56 fewer to 3 fewer) [Important]. **Necrotising enterocolitis (NEC)**: RCT: No significant reduction in NEC with larger dose (13 fewer per 1,000; 31 fewer to 10 more) [Important]. **Vitamin K** **Necrotising enterocolitis (NEC)**: RCT: No significant reduction in NEC with larger dose (35 fewer per 1,000; 87 fewer to 281 more) [Important]. **Vitamin B12 and folic acid** **Necrotising enterocolitis (NEC)**: RCT: No significant reduction in NEC with larger dose (59 fewer per 1,000; 87 fewer to 203 more). [Important] **Anaemia of prematurity**: RCT: No significant reduction in anaemia requiring transfusion (76 fewer per 1,000; 206 fewer to 215 more) [Important]. **Desirable effects for Māori** No additional evidence available	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no/lower vitamin intake	Risk difference with higher vitamin intake
Mortality: RCT: Vitamin C	130 (2 RCTs)	⨁◯◯◯ Very low[a,b,c,d]	**RR 1.99** (0.36 to 11.12)	Study population	
				30 per 1,000	**30 more per 1,000** (19 fewer to 307 more)
Mortality: RCT: Vitamin E	1602 (10 RCTs)	⨁⨁⨁◯ Moderate[e]	**RR 0.98** (0.80 to 1.20)	Study population	
				177 per 1,000	**4 fewer per 1,000** (35 fewer to 35 more)
Mortality: RCT: Vitamin D	187 (2 RCTs)	⨁◯◯◯ Very low[a,c,f,]	**RR 1.43** (0.32 to 6.39)	Study population	
				38 per 1,000	**17 more per 1,000** (26 fewer to 207 more)
Mortality: RCT: Vitamin A	2971 (14 RCTs)	⨁⨁⨁◯ Moderate[e,]	**RR 0.97** (0.80 to 1.18)	Study population	
				115 per 1,000	**3 fewer per 1,000** (23 fewer to 21 more)
Mortality: RCT: Vitamin B_{12} and folic acid	64 (1 RCT)	⨁◯◯◯ Very low[a,f,g,]	**RR 1.60** (0.29 to 8.92)	Study population	
				61 per 1,000	**36 more per 1,000** (43 fewer to 480 more)
Mortality: RCT: Vitamin K	75		**RR 1.43**	Study population	

	(1 RCT)	⨁◯◯◯ Very low[a,f,g]	(0.25 to 8.20)	59 per 1,000	**25 more per 1,000** (44 fewer to 424 more)
Neurodevelopmental impairment: RCT: Vitamin D assessed with: 22-26 months	78 (1 RCT)	⨁◯◯◯ Very low[e,g,h]	**RR 0.76** (0.46 to 1.27)	Study population	
				500 per 1,000	**120 fewer per 1,000** (270 fewer to 135 more)
Neurodevelopmental impairment: RCT: Vitamin D assessed with: Cognitive impairment (22-26 months)	70 (1 RCT)	⨁◯◯◯ Very low[e,g,h]	**RR 0.84** (0.45 to 1.58)	Study population	
				393 per 1,000	**63 fewer per 1,000** (216 fewer to 228 more)
Neurodevelopmental impairment: RCT: Vitamin D assessed with: Language impairment (22-26 months)	69 (1 RCT)	⨁◯◯◯ Very low[e,g,h]	**RR 0.80** (0.53 to 1.20)	Study population	
				643 per 1,000	**129 fewer per 1,000** (302 fewer to 129 more)
Neurodevelopmental impairment: RCT: Vitamin A assessed with: 18-22 months	538 (1 RCT)	⨁◯◯◯ Very low[c,e,g]	**RR 0.89** (0.74 to 1.08)	Study population	
				481 per 1,000	**53 fewer per 1,000** (125 fewer to 38 more)
Neurodevelopmental impairment: RCT: Vitamin A (assessed with: 18-22 months) assessed with: Cognitive impairment	539 (1 RCT)	⨁◯◯◯ Very low[ec,e,g]	**RR 0.83** (0.66 to 1.04)	Study population	
				388 per 1,000	**66 fewer per 1,000** (132 fewer to 16 more)
Neurodevelopmental impairment: RCT: Vitamin A (assessed with: 18-22 months) assessed with: Motor impairment	534 (1 RCT)	⨁◯◯◯ Very low[c,e,g]	**RR 0.83** (0.63 to 1.10)	Study population	
				297 per 1,000	**50 fewer per 1,000** (110 fewer to 30 more)
Neurodevelopmental impairment: RCT: Vitamin A (assessed with: 18-22 months) assessed with: bilateral blindness	577 (1 RCT)	⨁◯◯◯ Very low[d,g]	**RR 4.98** (0.24 to 103.33)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Neurodevelopmental impairment: RCT: Vitamin A (assessed with: 18-22 months) assessed with: Deafness	578 (1 RCT)	⨁◯◯◯ Very low[d,g]	**RR 1.24** (0.34 to 4.58)	Study population	
				14 per 1,000	**3 more per 1,000** (9 fewer to 50 more)
Neurodevelopmental impairment: RCT: Vitamin A (assessed with: 18-22 months) assessed with: Cerebral palsy	570 (1 RCT)	⨁◯◯◯ Very low[c,e,g,,]	**RR 0.83** (0.57 to 1.20)	Study population	
				180 per 1,000	**31 fewer per 1,000** (77 fewer to 36 more)
Adverse effects (prevention of unnecessary blood tests) - not measured	-	-	-	-	-
Faltering growth/body composition : RCT: Vitamin D assessed with: Weight (g.d-1)	81 (1 RCT)	⨁◯◯◯	-	The mean faltering growth/body composition : RCT: Vitamin D was not	MD **2 higher**

		Very low[c,e,g]		reported	(2.38 lower to 6.38 higher)
Faltering growth/body composition : RCT: Vitamin C assessed with: Weight (g.d-1)	50 (1 RCT)	⨁◯◯◯ Very low[a,d,g,]	-	The mean faltering growth/body composition : RCT: Vitamin C was not reported	MD **0.2 higher** (4.42 lower to 4.82 higher)
Retinopathy of prematurity: RCT: Vitamin A	1989 (11 RCTs)	⨁⨁◯◯ Low[a,k]	**RR 0.77** (0.61 to 0.98)	Study population	
				426 per 1,000	**98 fewer per 1,000** (166 fewer to 9 fewer)
Retinopathy of prematurity: RCT: Vitamin E	822 (5 RCTs)	⨁⨁◯◯ Low[a,e]	**RR 0.90** (0.73 to 1.11)	Study population	
				485 per 1,000	**49 fewer per 1,000** (131 fewer to 53 more)
Retinopathy of prematurity: RCT: Vitamin C	86 (1 RCT)	⨁◯◯◯ Very low[a,c,e,]	**RR 0.99** (0.57 to 1.72)	Study population	
				387 per 1,000	**4 fewer per 1,000** (166 fewer to 279 more)
Retinopathy of prematurity: RCT: Vitamin D	100 (1 RCT)	⨁◯◯◯ Very low[c,e,g]	**RR 0.79** (0.47 to 1.33)	Study population	
				500 per 1,000	**105 fewer per 1,000** (265 fewer to 165 more)
Bronchopulmonary dysplasia: RCT: Vitamin C	160 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	**RR 0.59** (0.37 to 0.93)	Study population	
				429 per 1,000	**176 fewer per 1,000** (270 fewer to 30 fewer)
Bronchopulmonary dysplasia: RCT: Vitamin E	1255 (6 RCTs)	⨁◯◯◯ Very low[e,j]	**RR 0.94** (0.79 to 1.12)	Study population	
				261 per 1,000	**16 fewer per 1,000** (55 fewer to 31 more)
Bronchopulmonary dysplasia: RCT: Vitamin A	2618 (12 RCTs)	⨁⨁◯◯ Low[a,e,]	**RR 0.89** (0.78 to 1.01)	Study population	
				589 per 1,000	**65 fewer per 1,000** (130 fewer to 6 more)
Bronchopulmonary dysplasia: RCT: Vitamin D	244 (3 RCTs)	⨁⨁◯◯ Low[j]	**RR 0.58** (0.41 to 0.83)	Study population	
				402 per 1,000	**169 fewer per 1,000** (237 fewer to 68 fewer)
Fully breastfed or breastmilk feeding at hospital discharge - not measured	-	-	-	-	-
Time to full enteral feeds - not measured	-	-	-	-	-
Duration of initial hospital stay - not measured	-	-	-	-	-

Sepsis: proven or suspected: RCT: Vitamin A assessed with: Culture proven	2244 (6 RCTs)	⨁⨁◯◯ Low[e,l]	**RR 0.88** (0.77 to 1.00)	Study population	
				237 per 1,000	**28 fewer per 1,000** (54 fewer to 0 fewer)
Sepsis: proven or suspected: RCT: Vitamin A assessed with: culture proven or suspected	2552 (8 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 0.88** (0.78 to 0.99)	Study population	
				254 per 1,000	**30 fewer per 1,000** (56 fewer to 3 fewer)
Sepsis: proven or suspected: RCT: Vitamin E assessed with: Proven	1031 (6 RCTs)	⨁⨁◯◯ Low[a,e]	**RR 1.34** (0.99 to 1.80)	Study population	
				126 per 1,000	**43 more per 1,000** (1 fewer to 101 more)
Sepsis: proven or suspected: RCT: Vitamin E	1121 (7 RCTs)	⨁⨁◯◯ Low[a,e]	**RR 1.15** (0.91 to 1.47)	Study population	
				184 per 1,000	**28 more per 1,000** (17 fewer to 87 more)
Sepsis: proven or suspected: RCT: Vitamin C assessed with: Culture proven	47 (1 RCT)	⨁◯◯◯ Very low[a,c,f]	**RR 0.66** (0.31 to 1.41)	Study population	
				458 per 1,000	**156 fewer per 1,000** (316 fewer to 188 more)
Sepsis: proven or suspected: RCT: Vitamin D assessed with: Proven	100 (1 RCT)	⨁◯◯◯ Very low[c,e,g]	**RR 0.68** (0.31 to 1.50)	Study population	
				139 per 1,000	**44 fewer per 1,000** (96 fewer to 69 more)
Necrotising enterocolitis: RCT: Vitamin B12 and folic acid	66 (1 RCT)	⨁◯◯◯ Very low[a,f,g]	**RR 0.35** (0.04 to 3.23)	Study population	
				91 per 1,000	**59 fewer per 1,000** (87 fewer to 203 more)
Necrotising enterocolitis: RCT: Vitamin K	75 (1 RCT)	⨁◯◯◯ Very low[a,f,g]	**RR 0.64** (0.11 to 3.87)	Study population	
				98 per 1,000	**35 fewer per 1,000** (87 fewer to 281 more)
Necrotising enterocolitis: RCT: Vitamin C	119 (1 RCT)	⨁◯◯◯ Very low[a,f,g]	**RR 1.27** (0.17 to 9.25)	Study population	
				25 per 1,000	**7 more per 1,000** (21 fewer to 206 more)
Necrotising enterocolitis: RCT: Vitamin D	100 (1 RCT)	⨁◯◯◯ Very low[d,g,]	**RR 1.63** (0.20 to 13.39)	Study population	
				28 per 1,000	**17 more per 1,000** (22 fewer to 344 more)
Necrotising enterocolitis: RCT: Vitamin E	1331 (8 RCTs)	⨁⨁◯◯ Low[a,e]	**RR 1.29** (0.90 to 1.85)	Study population	
				71 per 1,000	**21 more per 1,000**

					(7 fewer to 61 more)
Necrotising enterocolitis: RCT: Vitamin A	2626 (9 RCTs)	⨁⨁◯◯ Low[a,e,]	**RR 0.87** (0.69 to 1.10)	Study population	
				100 per 1,000	**13 fewer per 1,000** (31 fewer to 10 more)
Anaemia of prematurity: RCT: Vitamin E assessed with: Number of transfusion per infant	30 (1 RCT)	⨁◯◯◯ Very low[e,g,i,j,k,u]	-	The mean anaemia of prematurity: RCT: Vitamin E was not reported	MD **0.2 lower** (1.18 lower to 0.78 higher)
Anaemia of prematurity: RCT: Vitamin C assessed with: Number of transfusion per infant	51 (1 RCT)	⨁◯◯◯ Very low[a,c,g,]	-	The mean anaemia of prematurity: RCT: Vitamin C was not reported	MD **0.1 higher** (1.36 lower to 1.56 higher)
Anaemia of prematurity: RCT: Vitamin C assessed with: Number of infants requiring transfusions	81 (1 RCT)	⨁◯◯◯ Very low[d,g]	**RR 1.86** (0.50 to 6.92)	Study population	
				77 per 1,000	**66 more per 1,000** (38 fewer to 455 more)
Anaemia of prematurity: RCT: Vitamin B12 and folic acid assessed with: Anaemia of infants who required transfusion	64 (1 RCT)	⨁◯◯◯ Very low[a,e,g]	**RR 0.75** (0.32 to 1.71)	Study population	
				303 per 1,000	**76 fewer per 1,000** (206 fewer to 215 more)
Cost: cost of intervention, cost of neonatal care and life-long cost - not measured	-	-	-	-	-
Time to full sucking feeds (<0.5 days) - not measured	-	-	-	-	-

a. Downgraded one level for concerns about risk of bias
b. Downgraded one level for inconsistency
c. Downgraded one level for indirectness as population may not be generalisable
d. Downgraded three levels for imprecision with extremely wide confidence intervals crossing the line of no effect
e. Downgraded one level for imprecision due to confidence intervals crossing the line of no effect
f. Downgraded two levels for imprecision with very wide confidence intervals crossing the line of no effect
g. Downgraded one level for indirectness as evidence based on a single study
h. Downgraded one level for imprecision due to low event rates and/or small sample size
i. Downgraded one level as evidence is based on a single study
j. Downgraded two levels for concerns of risk of bias
k. Downgraded one level for inconsistency as I2 >50%
l. Downgraded one level for indirectness as the mode of administration is not generalisable

a)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial	**Vitamin A**	

○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Neurodevelopmental impairment:** RCT: No significant effect in bilateral blindness (RR 4.98; 0.24 to 103.33; unable to calculate absolute risk due to low events) and in deafness (3 more per 1,000; 9 fewer to 50 more) [Critical]. **Vitamin E** **Sepsis**: RCT: No significant increase in proven or suspected sepsis (28 more per 1,000; 17 fewer to 87 more) and proven sepsis with higher dose (43 more per 1,000; 1 fewer to 101 more) [Important]. **Necrotising enterocolitis (NEC)**: RCT: No significant increase in NEC with higher dose (21 more per 1,000; 7 fewer to 61 more) [Important]. **Vitamin C** **Mortality:** RCT: No significant increase in mortality with higher dose (30 more per 1,000; 19 fewer to 307 more) [Critical]. **Necrotising enterocolitis**: RCT: No significant increase in NEC with higher dose (7 more per 1,000; 21 fewer to 206 more) [Important]. **Anaemia of prematurity**: RCT: No significant effect on the number of transfusions per infant with higher dose (MD 0.1 transfusions higher; 1.36 lower to 1.56 higher) [Important]. **Anaemia of prematurity**: RCT: No significant increase in number of infants requiring transfusions with higher dose (66 more per 1,000; 38 fewer to 455 more) [Important]. **Vitamin D** **Mortality**: RCT: No significant increase in mortality with higher dose (17 more per 1,000; 26 fewer to 207 more) [Critical]. **Necrotising enterocolitis**: RCT: No significant increase in NEC with higher dose (17 more per 1,000; 22 fewer to 344 more) [Important]. **Vitamin K** **Mortality**: RCT: No significant increase in mortality with higher dosage (25 more per 1,000; 44 fewer to 424 more) [Critical]. **Vitamin B_{12} and folic acid** **Mortality**: RCT: No significant increase in mortality with higher dosage (36 more per 1,000; 43 fewer to 480 more) [Critical]. **Undesirable effects for Māori** No additional evidence available	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Moderate to very low certainty of evidence overall **Certainty of evidence for Māori** No additional evidence available	

Outcomes	Importance	Certainty of the evidence (GRADE)
Mortality: RCT: Vitamin C	CRITICAL	⨁◯◯◯ Very low
Mortality: RCT: Vitamin E	CRITICAL	⨁⨁⨁◯ Moderate
Mortality: RCT: Vitamin D	CRITICAL	⨁◯◯◯ Very low
Mortality: RCT: Vitamin A	CRITICAL	⨁⨁⨁◯ Moderate
Mortality: RCT: Vitamin B_{12} and folic acid	CRITICAL	⨁◯◯◯ Very low
Mortality: RCT: Vitamin K	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: Vitamin D assessed with : 22-26 months	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: Vitamin D assessed with: Cognitive impairment (22-26 months)	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: Vitamin D assessed with: Language impairment (22-26 months)	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: Vitamin A assessed with: 18-22 months	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: Vitamin A (assessed with: 18-22 months) assessed with: Cognitive impairment	CRITICAL	⨁◯◯◯ Very low

Neurodevelopmental impairment: RCT: Vitamin A (assessed with: 18-22 months) assessed with: Motor impairment	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: Vitamin A (assessed with: 18-22 months) assessed with: bilateral blindness	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: Vitamin A (assessed with: 18-22 months) assessed with: Deafness	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: Vitamin A (assessed with: 18-22 months) assessed with: Cerebral palsy	CRITICAL	⨁◯◯◯ Very low
Adverse effects (prevention of unnecessary blood tests) - not measured	IMPORTANT	-
Faltering growth/body composition: RCT: Vitamin D assessed with: Weight (g.d-1)	IMPORTANT	⨁◯◯◯ Very low
Faltering growth/body composition: RCT: Vitamin C assessed with: Weight (g.d-1)	IMPORTANT	⨁◯◯◯ Very low
Retinopathy of prematurity: RCT: Vitamin A	IMPORTANT	⨁⨁◯◯ Low
Retinopathy of prematurity: RCT: Vitamin E	IMPORTANT	⨁⨁◯◯ Low
Retinopathy of prematurity: RCT: Vitamin C	IMPORTANT	⨁◯◯◯ Very low
Retinopathy of prematurity: RCT: Vitamin D	IMPORTANT	⨁◯◯◯ Very low
Bronchopulmonary dysplasia: RCT: Vitamin C	IMPORTANT	⨁◯◯◯ Very low
Bronchopulmonary dysplasia: RCT: Vitamin E	IMPORTANT	⨁◯◯◯ Very low

Bronchopulmonary dysplasia: RCT: Vitamin A	IMPORTANT	⨁⨁◯◯ Low
Bronchopulmonary dysplasia: RCT: Vitamin D	IMPORTANT	⨁⨁◯◯ Low
Fully breastfed or breastmilk feeding at hospital discharge - not measured	IMPORTANT	-
Time to full enteral feeds - not measured	IMPORTANT	-
Duration of initial hospital stay - not measured	IMPORTANT	-
Sepsis: proven or suspected: RCT: Vitamin A assessed with: Culture proven	IMPORTANT	⨁⨁◯◯ Low
Sepsis: proven or suspected: RCT: Vitamin A assessed with: culture proven or suspected	IMPORTANT	⨁⨁⨁◯ Moderate
Sepsis: proven or suspected: RCT: Vitamin E assessed with: Proven	IMPORTANT	⨁⨁◯◯ Low
Sepsis: proven or suspected: RCT: Vitamin E	IMPORTANT	⨁⨁◯◯ Low
Sepsis: proven or suspected: RCT: Vitamin C assessed with: Culture proven	IMPORTANT	⨁◯◯◯ Very low
Sepsis: proven or suspected: RCT: Vitamin D assessed with: Proven	IMPORTANT	⨁◯◯◯ Very low
Necrotising enterocolitis: RCT: Vitamin B12 and folic acid	IMPORTANT	⨁◯◯◯ Very low
Necrotising enterocolitis: RCT: Vitamin K	IMPORTANT	⨁◯◯◯ Very low
Necrotising enterocolitis: RCT: Vitamin C	IMPORTANT	⨁◯◯◯ Very low

Necrotising enterocolitis: RCT: Vitamin D	IMPORTANT	⨁◯◯◯ Very low
Necrotising enterocolitis: RCT: Vitamin E	IMPORTANT	⨁⨁◯◯ Low
Necrotising enterocolitis: RCT: Vitamin A	IMPORTANT	⨁⨁◯◯ Low
Anaemia of prematurity: RCT: Vitamin E assessed with: Number of transfusion per infant	IMPORTANT	⨁◯◯◯ Very low
Anaemia of prematurity: RCT: Vitamin C assessed with: Number of transfusion per infant	IMPORTANT	⨁◯◯◯ Very low
Anaemia of prematurity: RCT: Vitamin C assessed with: Number of infants requiring transfusions	IMPORTANT	⨁◯◯◯ Very low
Anaemia of prematurity: RCT: Vitamin B12 and folic acid assessed with: Anaemia of infants who required transfusion	IMPORTANT	⨁◯◯◯ Very low
Cost: cost of intervention, cost of neonatal care and life-long cost - not measured	IMPORTANT	-
Time to full sucking feeds (<0.5 days) - not measured	NOT IMPORTANT	-

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	There is a high prevalence of maternal vitamin D deficiency in Aotearoa New Zealand. Because the prevalence of vitamin D deficiency is higher in Pacific people, supplementation might especially benefit Pacific infants. **Values for Māori** No evidence available.	**Critical outcomes** Mortality (<1 per 1000) Neurodevelopmental impairment (<10 per 1000)

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	**Vitamin C** **Higher versus no/lower dosage - very low certainty evidence** Reduction in bronchopulmonary dysplasia Uncertain effect on mortality, faltering growth/body composition, retinopathy of prematurity, sepsis, necrotising enterocolitis, anaemia of prematurity **Vitamin A** **Higher versus no/lower dosage - moderate certainty evidence** Reduced sepsis Uncertain effect on mortality **Higher versus no/lower dosage - low certainty evidence** Reduced retinopathy of prematurity Uncertain effect on bronchopulmonary dysplasia, necrotising enterocolitis, bronchopulmonary dysplasia, sepsis **Higher versus no/lower dosage - very low certainty evidence** Uncertain effect on neurodevelopmental impairment, cognitive impairment, motor impairment, bilateral blindness, deafness, cerebral palsy **Vitamin E** **Higher versus no/lower dosage - moderate certainty evidence** Uncertain effect on mortality **Higher versus no/lower dosage - low certainty evidence** Uncertain effect on retinopathy of prematurity, sepsis **Higher versus no/lower dosage - very low certainty evidence** Uncertain effect on anaemia of prematurity **Vitamin D** **Higher versus no/lower dosage - low certainty evidence** Reduction in bronchopulmonary dysplasia **Higher versus no/lower dosage - very low certainty evidence** Uncertain effect on mortality; neurodevelopmental impairment, cognitive and language	

	impairment, faltering growth/body composition, retinopathy of prematurity, sepsis, necrotising enterocolitis **Vitamin K** **Higher versus no/lower dosage - very low certainty evidence** Uncertain effect on mortality, necrotising enterocolitis **Vitamin B12 and folic acid** **Higher versus no/lower dosage - very low certainty evidence** Uncertain effect on mortality, necrotising enterocolitis, anaemia of prematurity **Balance of effects for Māori** No additional evidence	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Vitamin A 2 drops/kg/day (2 to 3 drops Optimus Vitamin A) $0.14 Vitamin D 1 drop/kg/day (2 to 3 drops Clinicians Vitamin D) $0.30 Vitamin E 7 mg/kg/day (7 to 10 mg) $0.12 Vitamin B1 Thiamine 200 µg/kg/day (200 to 300 µg) $0.05 Cost are small.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Costs are reasonably certain. **Certainty of evidence of required resources for Māori** No additional evidence available	

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	No economic studies were identified to address the cost-effectiveness of the higher or lower vitamin intake. **Cost effectiveness for Māori** No evidence available.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	**Equity for Māori** Our health system privileges whiteness with significant advantage experienced by non-Māori. Pēpi Māori are more likely to be born preterm, admitted to NICU, born at ELBW, and fewer survive. Preterm pēpi Māori are more likely to be vitamin deficient due to both biological and systemic factors, due to the social determinants of health and nutrition (e.g. colonisation, racism, income, education, employment and housing). Having more pigmented skin decreases the effectiveness of ultraviolet-induced vitamin D production, leading to lower vitamin D status compared with people with fairer skin. Neonatal and maternal plasma vitamin D concentration is significantly lower in infants with late-onset sepsis and with NEC, meaning that addressing vitamin D status has the potential to improve equity. Less is known about the deficiency of other vitamins in Māori. **Equity for Pacific families** A study of the nutritional status of 413 Auckland children aged 6-23 months found the prevalence of vitamin D deficiency varied with ethnicity: Pacific 24%, Māori 11%, European 3% and other ethnic groups 16%. Because the prevalence of vitamin D deficiency is higher in Pacific people, supplementation might especially benefit Pacific infants. While specific, up-to-date vitamin deficiency data in infants is limited, strong evidence from clinical and population health research points consistently to Māori and Pacific infants being disproportionately affected due to a combination of biological, social, and systemic factors. Pacific Island infants are over-represented in the preterm infant population and also at higher nutrient deficiency risk. **Equity for other underrepresented groups**	

	Indian infants are over-represented in the preterm infant population and also at higher nutrient deficiency risk. Based on presentations to Starship Child Health, a group at particular risk of symptomatic vitamin deficiency are Indian children from vegan families. Equity requires system-wide availability and clear, inclusive protocols that ensure every infant receives what they need from day one.	

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	The addition of some vitamins to enteral feeds is standard practice in Aotearoa New Zealand. Intramuscular vitamin A injections may not be acceptable to staff and parents. **Acceptability for Māori** No evidence available.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	The addition of some vitamins to enteral feeds is already standard practice in Aotearoa New Zealand. Intramuscular vitamin A injections may not be available to Aotearoa New Zealand hospitals. **Feasibility for Māori** No additional evidence available	

Summary of judgements

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

Type of recommendation

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
O	●	O	O	O

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