EtD 24. In preterm infants does fortified EBM vs. unfortified EBM lead to improved growth, neurodevelopment, clinical outcomes, fewer NEC cases, fewer gastrointestinal complications, less metabolic bone disease?

POPULATION:	Preterm infants
INTERVENTION:	Fortified expressed breastmilk
COMPARISON:	Unfortified expressed breastmilk
MAIN OUTCOMES:	**Critical outcomes** Mortality Necrotising enterocolitis Adverse effects – milk curd obstruction, metabolic bone disease Neurodevelopmental impairment Fully breastfed or breastmilk feeding at hospital discharge Faltering growth/body composition Time to full enteral feeds Duration of initial hospital stay Sepsis: proven or suspected **Important but not critical** Bronchopulmonary dysplasia Retinopathy of prematurity 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:	Expressed breastmilk is the preferred source of nutrition for preterm infants for who cannot yet breastfeed, due to its protective bioactive components, which support immune function, gastrointestinal maturation, and neurodevelopment. However, unfortified expressed breastmilk may not provide adequate amounts of protein, energy, and other key nutrients such as calcium, phosphorus and vitamins to meet the high nutritional demands of preterm infants. Fortifying expressed breastmilk with commercial multicomponent breastmilk fortifiers aims to address these deficits by providing most of the additional nutrients to support growth and development in one nutritional supplement. Fortified expressed breastmilk has been associated with improved growth compared to unfortified expressed breastmilk. This is particularly important for preterm infants, who are at high risk of faltering growth and neurodevelopmental impairment. Furthermore, fortified expressed breastmilk may help reduce the risk of metabolic bone disease/rickets of prematurity, a common complication caused by low body stores and inadequate vitamin D, calcium and phosphorus intake. The additional nutrients in fortified expressed breastmilk are also thought to support better clinical outcomes by improving overall nutritional status. Concerns about breastmilk fortifiers

	include possible increased risk of necrotising enterocolitis or milk curd obstruction associated with cow's milk-based (bovine) fortifiers and some preterm infants struggle with feeding intolerance or gastrointestinal issues when using fortifiers. There are also concerns that the process of adding fortifier to breastmilk can alter the composition and benefits of breastmilk and concerns about the safety of storing fortified breastmilk in a fridge and for how long it can safely be stored.
CONFLICT OF INTERESTS:	The following case-control study of milk curd obstruction (Reference 2) co-authors are on the Guideline Development Group: Barbara Cormack, Frank Bloomfield. Frank Bloomfield supervised the first author. \ The following 2020 Cochrane systematic review (Brown *et al*) co-author wrote this Evidence to Decision document: Julie Brown

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	In preterm infants, high serum alkaline phosphatase concentration, especially above 500 IU/L, is associated with an increased risk of metabolic bone disease and low bone mineralisation, potentially leading to metabolic bone disease (osteopenia or rickets of prematurity). Serum alkaline phosphatase evidence is based on a systematic review [1] and a case-control study [2] **Necrotising enterocolitis (NEC)**: RCT: No significant reduction in NEC overall (9 more per 1,000; 7 fewer to 42 more) and for very preterm of VLBW infants (7 more per 1,000; 11 fewer to 47 more) [Critical]. **Adverse effects**: RCT: large increase in bone mineral density for fortified breastmilk MD 12 higher mg/cm; 6.28 higher to 17.72 higher). No difference in the prevalence of milk curd obstruction between fortified and unfortified breastmilk [Critical]. **Adverse effects**: Large reduction in ALP for fortified breastmilk (MD 141.93 lower; 203.93 lower to 79.92 lower) [Critical]. **Neurodevelopmental impairment:** RCT: No significant difference between fortified and unfortified feeds for Bayley II Psychomotor Development Index (MD 2.4 points higher; 1.9 lower to 6.7 higher) or Mental Bayley II Development Index (MD 2.2 points higher; 3.35 lower to 7.75 higher) at 18 months [Critical]. **No faltering growth/body composition:** RCT: Moderate increase in weight gain overall for fortified breastmilk (MD 1.76 g/kg/day higher; 1.3 higher to 2.22 higher); large increase in weight gain for very preterm or VLBW infants (MD 2.18 g/kg/day higher; 1.54 higher to 2.81 higher). Small increase in length overall for fortified breastmilk (MD 0.11 cm/week higher; 0.08 higher to 0.15 higher); small increase in length for very preterm or VLBW infants (MD 0.16 cm/week higher; 0.11 higher to 0.2 higher). Small increase in head circumference overall for	**Population information for included evidence** Cochrane review by Walsh 2019 [3] Median birthweight was 823 and 849 g for cases and controls, respectively, and median gestational age was 26 weeks for both groups. Brown *et al* Cochrane review [1]: 11 trials included only very preterm or VLBW infants. One trial included 'healthy preterm infants' but gave no birthweight criteria and the upper birthweight eligibility criteria for the remaining 6 studies ranged from 1600 - 2000 g. Studies included mother's own milk, donor milk or a mixture, or formula as a supplement.

	fortified breastmilk (MD 0.06 cm/week higher; 0.03 higher to 0.08 higher); small increase in head circumference for very preterm or VLBW infants (MD 0.07 cm/week higher; 0.03 higher to 0.11 higher). Little or no effect in weight (MD 0.03 kg lower; 0.31 lower to 0.25 higher); length (MD 0.19 cm lower; 0.98 lower to 0.6 higher) and head circumference (MD 0.1 cm lower; 0.37 lower to 0.18 higher) for fortified breastmilk at 12-18 months [Critical]. **Duration of initial hospital stay**: RCT: No significant effect on duration of hospital stay overall for fortified milk (MD 0.07 weeks lower; 0.35 lower to 0.21 higher). Small reduction on duration of hospital stay for very preterm of VLBW infants (MD 0.48 days lower; 0.89 lower to 0.08 lower) [Critical]. **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 unfortified expressed breastmilk	Risk difference with fortified expressed breastmilk
Mortality - not measured	-	-	-	-	-
Necrotising enterocolitis: RCT	1110 (6 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 1.37** (0.72 to 2.63)	Study population	
				26 per 1,000	**9 more per 1,000** (7 fewer to 42 more)
Necrotising enterocolitis: RCT: Very preterm or VLBW	701 (8 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 1.28** (0.55 to 2.99)	Study population	
				23 per 1,000	**7 more per 1,000** (11 fewer to 47 more)
Adverse effects: RCT assessed with: Serum alkaline phosphatase (IU/L)	363 (6 RCTs)	⨁◯◯◯ Very low[a,c]	-	The mean adverse effects: RCT serum alkaline phosphatase was **812.3 IU/L**	MD **141.93 lower** (203.93 lower to 79.92 lower)
Adverse effects: RCT assessed with: Bone mineral content (mg/cm)	59 (1 RCT)	⨁◯◯◯ Very low[a,d]	-	The mean adverse effects: RCT was **47 mg/cm**	MD **12 higher** (6.28 higher to 17.72 higher)
Adverse effects: Retrospective case control study assessed with: Milk curd obstruction	20 cases 40 controls (1 non-randomised study)	⨁◯◯◯ Very low[d,e]	-	8/20 (40%) of infants with milk curd obstruction had bovine derived multicomponent fortified human breastmilk and 27/40 (68%) of controls had bovine derived multicomponent fortified human breastmilk. p=0.08	
Neurodevelopmental impairment: RCT assessed with: Bayley II Psychomotor development index at 18 months [measurement scale not specified in review]	245 (1 RCT)	⨁◯◯◯ Very low[a,c,d]	-	The mean neurodevelopmental impairment: RCT: Bayley II Psychomotor Development Index was **89.9 points**	MD **2.4 higher** (1.9 lower to 6.7 higher)
Neurodevelopmental impairment: RCT assessed with: Bayley II Mental development index	245 (1 RCT)	⨁◯◯◯ Very low[a,c,d]	-	The mean neurodevelopmental impairment: RCT: Bayley II Mental Development Index was **103.8 points**	MD **2.2 higher** (3.35 lower to 7.75 higher)

at 18 months [measurement scale not specified in review]					
Fully breastfed or breastmilk feeding at hospital discharge: RCT - not measured	-	-	-	-	-
Faltering growth/body composition: RCT assessed with: Weight gain (g/kg/day)	951 (14 RCTs)	⨁⨁◯◯ Low[a,f]	-	The mean faltering growth/body composition: RCT was **15.12 g/kg/day**	MD **1.76 higher** (1.3 higher to 2.22 higher)
Faltering growth/body composition: RCT: Very preterm or VLBW assessed with: Weight gain (g/kg/day)	505 (8 RCTs)	⨁⨁◯◯ Low[a,f]	-	The mean faltering growth/body composition: RCT: Very preterm or VLBW was **15.93 g/kg/day**	MD **2.18 higher** (1.54 higher to 2.81 higher)
Faltering growth/body composition: RCT assessed with: Length (cm/week)	741 (10 RCTs)	⨁⨁◯◯ Low[a,f]	-	The mean faltering growth/body composition: RCT was **0.84 cm/week**	MD **0.11 higher** (0.08 higher to 0.15 higher)
Faltering growth/body composition: RCT: Very preterm or VLBW assessed with: Length (cm/week)	375 (5 RCTs)	⨁⨁◯◯ Low[a,f]	-	The mean faltering growth/body composition: RCT: Very preterm or VLBW was **0.85 cm/week**	MD **0.16 higher** (0.11 higher to 0.2 higher)
Faltering growth/body composition: RCT assessed with: Head growth (cm/week)	821 (11 RCTs)	⨁⨁⨁◯ Moderate[a]	-	The mean faltering growth/body composition: RCT was **0.83 cm/week**	MD **0.06 higher** (0.03 higher to 0.08 higher)
Faltering growth/body composition: RCT: Very preterm or VLBW assessed with: Head growth (cm/week)	375 (5 RCTs)	⨁⨁◯◯ Low[a,f]	-	The mean faltering growth/body composition: RCT: Very preterm or VLBW was **0.88 cm/week**	MD **0.07 higher** (0.03 higher to 0.11 higher)
Faltering growth/body composition: RCT assessed with: Weight at 12-18 months (kg)	270 (2 RCTs)	⨁⨁◯◯ Low[a,b]	-	The mean faltering growth/body composition: RCT was **9.55 kg**	MD **0.03 lower** (0.31 lower to 0.25 higher)
Faltering growth/body composition: RCT assessed with: Length at 12-18 months (cm)	270 (2 RCTs)	⨁⨁◯◯ Low[a,b]	-	The mean faltering growth/body composition: RCT was **78 cm**	MD **0.19 lower** (0.98 lower to 0.6 higher)
Faltering growth/body composition: RCT assessed with: Head circumference at 12-18 months (cm)	270 (2 RCTs)	⨁⨁◯◯ Low[a,b]	-	The mean faltering growth/body composition: RCT was **47.5 cm**	MD **0.1 lower** (0.37 lower to 0.18 higher)
Time to full enteral feeds - not measured	-	-	-	-	-
Duration of initial hospital stay: RCT assessed with: Weeks	526 (6 RCTs)	⨁◯◯◯ Very low[a,b,f]	-	The mean duration of initial hospital stay: RCT was **4.64 weeks**	MD **0.07 lower** (0.35 lower to 0.21 higher)
Duration of initial hospital stay: RCT: Very preterm or VLBW assessed with: Weeks	236 (3 RCTs)	⨁⨁⨁◯ Moderate[a]	-	The mean duration of initial hospital stay: RCT: Very preterm or VLBW was **4.73 weeks**	MD **0.48 lower** (0.89 lower to 0.08 lower)
Sepsis: proven or suspected - not measured	-	-	-	-	-
Bronchopulmonary dysplasia - not measured	-	-	-	-	-

Retinopathy of prematurity - not measured	-	-	-	-	-
Anaemia of prematurity - not measured	-	-	-	-	-
Cost: cost of intervention, cost of neonatal care and life-long cost - not measured	-	-	-	-	-
Time to full sucking feeds - not measured	-	-	-	-	-

a. Downgraded one level for risk of bias
b. Downgraded one level for imprecision with confidence intervals crossing the line of no effect
c. Downgraded two levels for imprecision with wide confidence intervals crossing the line of no effect
d. Downgraded one level for indirectness as evidence based on a single trial
e. Downgraded two levels for risk of bias as evidence is based on a single retrospective case-control study of a rare event
f. Downgraded one level as heterogeneity was high between I2 =60-80%

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	If breastmilk fortifiers are not used, several nutrients need to be added to breastmilk individually at most feeds. The addition of these individual nutrients (energy, protein, fat, carbohydrate, vitamins, iron, calcium, phosphorus zinc and folic acid) adds to the risk of sepsis and feed intolerance. **Undesirable effects for Māori** No additional evidence available	A family may have a negative, or uncertain response to fortification as a concept and require time to engage with the approach and ask questions. Careful communication to the family re: the possible risks in accessible terminology e.g. rickets of prematurity etc. is advised.

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 - not measured	CRITICAL	-

Necrotising enterocolitis: RCT	CRITICAL	⨁⨁◯◯ Low
Necrotising enterocolitis: RCT: Very preterm or VLBW	CRITICAL	⨁⨁◯◯ Low
Adverse effects: RCT assessed with: Serum alkaline phosphatase (IU/L)	CRITICAL	⨁◯◯◯ Very low
Adverse effects: RCT assessed with: Bone mineral content (mg/cm)	CRITICAL	⨁◯◯◯ Very low
Adverse effects: Retrospective case control study assessed with: Milk curd obstruction	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT assessed with: Psychomotor development index at 18 months [measurement scale not specified in review]	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT assessed with: Mental development index at 18 months [measurement scale not specified in review]	CRITICAL	⨁◯◯◯ Very low
Fully breastfed or breastmilk feeding at hospital discharge: RCT - not measured	CRITICAL	-
Faltering growth/body composition: RCT assessed with: Weight gain (g/kg/day)	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT: Very preterm or VLBW assessed with: Weight gain (g/kg/day)	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT assessed with: Length (cm/week)	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT: Very preterm or VLBW assessed with: Length (cm/week)	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT assessed with: Head growth (cm/week)	CRITICAL	⨁⨁⨁◯ Moderate
Faltering growth/body composition: RCT: Very preterm or VLBW assessed with: Head growth (cm/week)	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT assessed with: Weight at 12-18 months (kg)	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition: RCT assessed with: Length at 12-18 months (cm)	CRITICAL	⨁⨁◯◯ Low

Faltering growth/body composition: RCT assessed with: Head circumference at 12-18 months (cm)	CRITICAL	⨁⨁◯◯ Low
Time to full enteral feeds - not measured	CRITICAL	-
Duration of initial hospital stay: RCT assessed with: Weeks	CRITICAL	⨁◯◯◯ Very low
Duration of initial hospital stay: RCT: Very preterm or VLBW assessed with: Weeks	CRITICAL	⨁⨁⨁◯ Moderate
Sepsis: proven or suspected - not measured	CRITICAL	-
Bronchopulmonary dysplasia - not measured	IMPORTANT	-
Retinopathy of prematurity - not measured	IMPORTANT	-
Anaemia of prematurity - not measured	IMPORTANT	-
Cost: cost of intervention, cost of neonatal care and life-long cost - not measured	IMPORTANT	-
Time to full sucking feeds - 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	Duration of hospital stay is important to families (and has a wide impact on a range of factors for whānau depending upon overall duration, location(s) etc). From a parent's perspective weight gain can be seen as a cornerstone of their infant's progress as is full sucking feeds at discharge. Again, careful management is needed to ensure good information is communicated as to why these things may not be seen as crucial in the grand scheme of optimal nutritional management.	Sepsis is a huge concern for parents.

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	**Fortified compared with unfortified breastmilk - Moderate certainty evidence** No faltering growth/body composition (increase in head circumference) Shorter duration of hospital stay for very preterm or VLBW infants **Fortified compared with unfortified breastmilk - Low certainty evidence** No faltering growth/body composition (increase in weight gain, length, head circumference) Uncertain effect for NEC; faltering growth/body composition (weight gain, length, head circumference at 12-18 months) **Fortified compared with unfortified breastmilk -Very low certainty evidence** Increased bone mineral density Uncertain effect for neurodevelopmental impairment at 18 months, serum alkaline phosphatase, duration of initial hospital stay **Balance of effects for Māori** No additional evidence available.	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Breastmilk fortifier** $3.75 per 100 mL **Costs (for up to 100-120 days)** Breastmilk fortifier $3.75 per 100 mL at 180 mL/kg/day ($5.80 to $9 per day) **Cost difference for fortified vs. unfortified breastmilk is** approx. $580 to $900 per baby per admission of 100 days, (Large). **Labour to add a fortifier to breastmilk by parent or nurse is minimal** Labour to add a fortifier to breastmilk in a central milk preparation facility is higher However, if fortifier is not used, some or all of the following nutrients will need to be added to enteral feeds: **Energy supplementation** 3.6 to 6.8 mL/kg/day Calogen (long-chain triglyceride emulsion) **Dose per baby per day** 5 to 10 mL Calogen **Cost per day** Calogen $0.40 to $0.80 **Cost per admission per infant (up to 100 days)** Calogen $40 to 80 **Nutrient cost per day to replace nutrients in breastmilk fortifier**	

	Vitamin A 2 drops/kg/d (2 to 3 drops Optimus Vitamin A) $0.14 Vitamin D 1 drop/kg/d (2 to 3 drops Clinicians Vitamin D) $0.30 Vitamin E 7 mg/kg/d (7 to 10 mg) $0.12 Thiamine 200 µg/kg/d (200 to 300 µg) $0.05 Folic acid 50 µg/kg/d (50 to 100 50 µg) $0.06 Calcium 2.6 mmol/kg/d (2.6 to 3.9 mmol $2.60 Phosphorus 2.6 mmol/kg/d (2.6 to 3.9 mmol) $0.82 Iron 3 mg/kg/d (3 to 4.5 mg) $0.02 Zinc 2 mg/kg/d (2 to 3 mg) $0.10 Sodium 3 mmol/kg/d (3 to 4.5 mmol) $0.80 Potassium 2 mmol/kg/d (2 to 3 mmol) $0.88 Iodine 50 µg/kg/d. (50 to 75 µg) $0.07 **Total $5.95 per day** **Resources required for Māori** Not different	

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 costs for Māori** No additional evidence available.	Aotearoa New Zealand Breastmilk fortifier $3.75 per 100 mL

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	There are no studies that assess the specific cost-effectiveness of fortified expressed breastmilk compared with unfortified expressed breastmilk, particularly in the context of preterm infants. **Cost effectiveness for Māori**	

comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	No additional 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** Māori preterm pēpi are likely at increased risk of deficiencies of the vitamins and micronutrients supplied by breastmilk fortifier, due to the social determinants of health and nutrition (e.g. colonisation, racism, income, education, employment and housing) and therefore would benefit more from the use of breastmilk fortifiers. 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%. To date, no large Aotearoa New Zealand studies have measured vitamin D levels specifically in Māori preterm pēpi; however, based on adult and toddler data and considering skin tone and lack of sun exposure during NICU care, they are considered high-risk. **Equity for Pacific families** Pacific Island infants are overrepresented in the preterm infant population and also at higher nutrient deficiency risk. A study of vitamin D status of exclusively breastfed infants in Auckland aged 2-3 months found 24% were vitamin D deficient (25(OH)D <27.5nmol/L). Pacific infants may not consistently receive breastmilk fortification due to variable practice across hospitals and limited staff training in cultural engagement. Pacific families may not understand why fortifiers are needed if explanations are not provided in a culturally meaningful way. Equity requires clear guidance and inclusive conversations about infant nutrition. **Equity for underrepresented groups** Indian infants are overrepresented in the preterm infant population and also at higher nutrient deficiency risk. A study of vitamin D status of exclusively breastfed infants in Auckland aged 2-3 months found 24% were vitamin D deficient (25(OH)D <27.5nmol/L). A group at particular risk of symptomatic nutrient deficiency presenting to Starship Child Health are Indian children from vegan families. Migrant, refugee and rural families may not receive timely or adequate explanations about the role of fortifiers, especially when language or literacy barriers exist. This can lead to mistrust or passive consent. Equity means ensuring all families have access to understandable information and	

	consistent nutritional care regardless of setting.	

Acceptability
Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Breastmilk fortifier is widely used in Aotearoa New Zealand neonatal units so probably will be accepted. **Acceptability for Māori** No additional evidence available.	Bovine based fortifier may not be acceptable to vegans.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Breastmilk fortifier is widely used in Aotearoa New Zealand neonatal units so will be feasible. **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
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			

	JUDGEMENT						
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
○	○	○	●	○

References

1. Brown, J.V.; Lin, L.; Embleton, N.D.; Harding, J.E.; McGuire, W. Multinutrient fortification of human milk for preterm infants. *Cochrane Database Syst. Rev.* **2020**, *6*, doi:10.1002/14651858.CD000343.pub4.
2. Walsh, O.; Anthony, R.; Wang, Z.; Cormack, B.E.; Bloomfield, F.H. Case-control study of milk curd obstruction in newborn infants in a tertiary surgical neonatal intensive care unit. *Arch Dis Child Fetal Neonatal Ed* **2024**, doi:10.1136/archdischild-2024-327565.
3. Walsh, V.; Brown, J.V.E.; Askie, L.M.; Embleton, N.D.; McGuire, W. Nutrient-enriched formula versus standard formula for preterm infants. *Cochrane Database Syst. Rev.* **2019**, *7*, Cd004204, doi:10.1002/14651858.CD004204.pub3.

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