EtD 28. Should human-based fortifier vs. bovine-based fortifier be used in preterm infants?

POPULATION:	Preterm infants
INTERVENTION:	Human milk-based fortifier
COMPARISON:	Bovine milk-based fortifier
MAIN OUTCOMES:	**Critical for making a decision** Mortality Neurodevelopmental impairment Necrotising enterocolitis (NEC) Adverse effects Fully breastmilk feeding at hospital discharge Faltering growth/body composition **Important but not critical** Duration of initial hospital stay Time to full enteral feeds Bronchopulmonary dysplasia Sepsis: proven or suspected Retinopathy of prematurity Anaemia of prematurity Cost: cost of intervention, cost of neonatal care and life-long cost **Of limited importance** Time to full sucking feeds
SETTING:	Neonatal care
PERSPECTIVE:	Clinical guideline recommendation - patient perspective
BACKGROUND:	For very preterm infants, mother's own breastmilk is the preferred feed, but multinutrient fortifiers are needed to meet their recommended nutritional requirements. Most fortifiers are bovine (cow's) milk-based, but with the increasing use of donor breastmilk, interest has grown in using multinutrient fortifiers derived from human milk. Research suggests a potential link between bovine-derived products and higher NEC risk, prompting the development of human milk-derived fortifiers, despite their high cost. These fortifiers are currently available in North America, the UK and Australia, but regulations, policies and ethical concerns regarding the commercialisation of human milk vary globally. The evidence supporting human milk-based fortifiers is limited, relying on a few randomised trials and observational studies. Given the importance of NEC as a cause of serious morbidity and mortality worldwide, the large costs associated with human-derived products to society along with the ethical issues raised, there is an urgent need to systematically review the evidence base for using human milk-derived fortifiers.
CONFLICT OF	None

INTERESTS:	

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	We pooled data on 8 RCTs [1-8]. **Necrotising enterocolitis (NEC)**: RCT: No significant reduction on NEC ≥ stage 2 (37 fewer per 1,000; 60 fewer to 3 more) or for surgical NEC (29 fewer per 1,000; 44 fewer to 8 more) [Critical]. **No faltering growth/body composition**: RCT: No significant effect on length increment (MD 0.16 cm/week lower; 0.33 lower to 0.01 higher); length on day 21 (MD 0.91 cm lower; 2.17 lower to 0.35 higher); rate of weight gain (MD 0.76 g/kg/day lower; 2.34 lower to 0.83 higher); weight on day 21 (MD 113.2 g lower; 276.33 lower to 49.93 higher); growth in head circumference (MD 0.04 cm/week higher; 0.11 lower to 0.2 higher); head circumference on day 21 (MD 0.15 cm higher; 1.2 lower to 1.5 higher) [Critical]. **Time to reach full enteral feeds**: RCT: Time to reach full enteral feeds (150 mL/kg/day) was a median of 10 days in both groups. Human milk fortification (n=115) median 10 days (IQR 8-15); Bovine milk fortification (n=113) median 10 days (IQR 7-15) [Important]. **Bronchopulmonary dysplasia**: RCT: No significant reduction in bronchopulmonary dysplasia (51 fewer per 1,000; 133 fewer to 57 more) [Important]. **Retinopathy of prematurity**: RCT: No significant reduction in retinopathy of prematurity (8 fewer per 1,000; 61 fewer to 56 more) [Important]. **Desirable effects for Māori** No additional evidence is available.	**Population information for included evidence** Italy: RCT [1]: Low birthweight infants. UK: RCT [2]: Infants <30 weeks' gestational age. UK: RCT [3]: <32 weeks' gestation or <1500 g who had reached full enteral feeds. Sweden: RCT [4]: Extremely preterm infants born between gestational week 22 + 0 and 27 + 6 fed exclusively human breastmilk. Brazil: RCT [5]: Very low birthweight infants. Canada: RCT [6]: Infants born <1250 g. Sweden/Italy: RCT [7]: Preterm infants with birthweights ranging from 940 g to 1750 g. USA: RCT [8]: Extremely premature infants birthweight 500 to 1250 g

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with bovine-based fortifier	Risk difference with E.G. 2.4 human-based fortifier
Mortality: RCT	714 (5 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 0.72** (0.42 to 1.23)	Study population	
				84 per 1,000	**24 fewer per 1,000** (49 fewer to 19 more)
Neurodevelopmental impairment: RCT assessed with: Bayley III Cognitive score <85	116 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	**RR 1.09** (0.56 to 2.12)	Study population	
				222 per 1,000	**20 more per 1,000**

					(98 fewer to 249 more)
Neurodevelopmental impairment: RCT assessed with: Bayley III language score <85	113 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	**RR 0.89** (0.56 to 1.43)	Study population	
				404 per 1,000	**44 fewer per 1,000** (178 fewer to 174 more)
Neurodevelopmental impairment: RCT: RCT assessed with: Bayley III Motor score < 85	115 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	**RR 1.03** (0.52 to 2.04)	Study population	
				222 per 1,000	**7 more per 1,000** (107 fewer to 231 more)
Neurodevelopmental impairment: RCT assessed with: Bayley III Cognitive score <70	116 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	**RR 0.87** (0.37 to 2.04)	Study population	
				167 per 1,000	**22 fewer per 1,000** (105 fewer to 173 more)
Neurodevelopmental impairment: RCT assessed with: Bayley III Language score <70	113 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	**RR 0.93** (0.45 to 1.93)	Study population	
				212 per 1,000	**15 fewer per 1,000** (116 fewer to 197 more)
Neurodevelopmental impairment: RCT assessed with: Bayley III Motor score <70	115 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	**RR 0.71** (0.30 to 1.66)	Study population	
				185 per 1,000	**54 fewer per 1,000** (130 fewer to 122 more)
Necrotising enterocolitis >/= 2: RCT	600 (4 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 0.59** (0.34 to 1.03)	Study population	
				91 per 1,000	**37 fewer per 1,000** (60 fewer to 3 more)
Necrotising enterocolitis surgical: RCT	463 (3 RCTs)	⨁⨁◯◯ Low[a,d]	**RR 0.49** (0.21 to 1.14)	Study population	
				56 per 1,000	**29 fewer per 1,000** (44 fewer to 8 more)
Adverse effect: RCT: Feeding interruption	353 (2 RCTs)	⨁◯◯◯ Very low[a,c]	**RR 0.99** (0.76 to 1.28)	Study population	
				391 per 1,000	**4 fewer per 1,000** (94 fewer to 109 more)
Adverse effects: Metabolic bone disease of prematurity - not measured	-	-	-	-	-
Fully breastmilk feeding at hospital discharge: RCT assessed with: Mothers own milk at discharge	28 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	**RR 0.64** (0.35 to 1.15)	Study population	
				786 per 1,000	**283 fewer per 1,000** (511 fewer to 118 more)
Faltering growth / body composition: RCT: Length increment assessed with: (cm/week)	75 (2 RCTs)	⨁⨁◯◯ Low[a,e]	-	The mean faltering growth / body composition: RCT: Length increment was **1.18 cm/week**	MD **0.16 lower** (0.33 lower to 0.01 higher)

Faltering growth / body composition: RCT: Length Day 21 assessed with: (cm)	40 (1 RCT)	⨁◯◯◯ Very low[a,b,e]	-	The mean faltering growth / body composition: RCT: Length Day 21 was **42.05 cm**	MD **0.91 lower** (2.17 lower to 0.35 higher)
Faltering growth / body composition: RCT: Weight Day 21 assessed with: (g)	40 (1 RCT)	⨁◯◯◯ Very low[a,b,f]	-	The mean faltering growth / body composition: RCT: Weight Day 21 was **1,678.5 g**	MD **113.2 lower** (276.33 lower to 49.93 higher)
Faltering growth / body composition: RCT: Rate of weight gain assessed with: (g/kg/day)	282 (3 RCTs)	⨁◯◯◯ Very low[a,c]	-	The mean faltering growth / body composition: RCT: Rate of weight gain was **17.06 g/kg/day**	MD **0.76 lower** (2.34 lower to 0.83 higher)
Faltering growth / body composition: RCT: Growth in head circumference assessed with: (cm/week)	75 (2 RCTs)	⨁⨁◯◯ Low[a,e]	-	The mean faltering growth / body composition: RCT: Growth in head circumference was **0.88 cm/week**	MD **0.04 higher** (0.11 lower to 0.2 higher)
Faltering growth / body composition: RCT: Head circumference Day 21 (cm) assessed with: (cm)	40 (1 RCT)	⨁⨁◯◯ Low[a,b]	-	The mean faltering growth / body composition: RCT: Head circumference Day 21 (cm) was **28.39 cm**	MD **0.15 higher** (1.2 lower to 1.5 higher)
Duration of hospital stay - not reported	-	-	-	-	-
Time to reach full enteral feeds: RCT	228 (1 RCT)	⨁⨁◯◯ Low[a,b]	-	Time to reach full enteral feeds, 150 mL/kg/day (days) - Human milk fortification (n=115) median 10 days (IQR 8-15) Bovine milk fortification (n=113) median 10 days (IQR 7-15)	
Bronchopulmonary dysplasia: RCT	543 (4 RCTs)	⨁◯◯◯ Very low[a,c]	**RR 0.92** (0.79 to 1.09)	Study population	
				632 per 1,000	**51 fewer per 1,000** (133 fewer to 57 more)
Confirmed and suspected sepsis: RCT	754 (6 RCTs)	⨁◯◯◯ Very low[a,c]	**RR 1.03** (0.77 to 1.39)	Study population	
				188 per 1,000	**6 more per 1,000** (43 fewer to 73 more)
Retinopathy of prematurity: RCT	705 (5 RCTs)	⨁◯◯◯ Very low[a,b]	**RR 0.97** (0.77 to 1.21)	Study population	
				267 per 1,000	**8 fewer per 1,000** (61 fewer to 56 more)
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 concerns for risk of bias

b. Downgraded one level for indirectness as evidence is based on a single study
c. Downgraded two levels for imprecision due to very wide confidence intervals that cross the line of no effect
d. Downgraded one level for inconsistency as I2 is 50-80%
e. Downgraded one level for imprecision as confidence intervals cross the line of no effect
f. Downgraded three levels for imprecision with extremely wide confidence intervals crossing the line of no effect

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Mortality**: RCT: No significant reduction in mortality for human-based fortifier (24 fewer per 1,000; 49 fewer to 19 more) [Critical]. **Neurodevelopmental impairment**: RCT: No significant effect on Bayley III Cognitive score <85 (20 more per 1,000; 98 fewer to 249 more); Bayley III Language score <85 (44 fewer per 1,000; 178 fewer to 174 more); Bayley III Motor score < 85 (7 more per 1,000; 107 fewer to 231 more); Bayley III Cognitive score <70 (22 fewer per 1,000; 105 fewer to 173 more); Bayley III Language score <70 (15 fewer per 1,000; 116 fewer to 197 more) and Bayley III Motor score <70 (54 fewer per 1,000; 130 fewer to 122 more) [Critical]. **Adverse effect**: RCT: No significant effect on feeding interruptions (4 fewer per 1,000; 94 fewer to 109 more) [Critical]. **Fully breastmilk feeding at hospital discharge**: RCT: No significant reduction in fully breastmilk feeding at discharge (283 fewer per 1,000; 511 fewer to 118 more) [Critical]. **Sepsis**: RCT: No significant effect on sepsis (6 more per 1,000; 43 fewer to 73 more) [Important]. **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	CRITICAL	⨁⨁⨁◯ Moderate
Neurodevelopmental impairment: RCT assessed with: Bayley III Cognitive score <85	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT assessed with: Bayley III language score <85	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT: RCT assessed with: Bayley III Motor score < 85	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT assessed with: Bayley III Cognitive score <70	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT assessed with: Bayley III Language score <70	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT assessed with: Bayley III Motor score <70	CRITICAL	⨁◯◯◯ Very low
Necrotising enterocolitis >/= 2: RCT	CRITICAL	⨁⨁⨁◯ Moderate
Necrotising enterocolitis surgical: RCT	CRITICAL	⨁⨁◯◯ Low
Adverse effect: RCT: Feeding interruption	CRITICAL	⨁◯◯◯ Very low
Adverse effects: Metabolic bone disease of prematurity - not measured	CRITICAL	-
Fully breastmilk feeding at hospital discharge: RCT assessed with: Mothers own milk at discharge	CRITICAL	⨁◯◯◯ Very low

Faltering growth / body composition: RCT: Length increment assessed with: (cm/week)	CRITICAL	⨁⨁◯◯ Low
Faltering growth / body composition: RCT: Length Day 21 assessed with: (cm)	CRITICAL	⨁◯◯◯ Very low
Faltering growth / body composition: RCT: Weight Day 21 assessed with: (g)	CRITICAL	⨁◯◯◯ Very low
Faltering growth / body composition: RCT: Rate of weight gain assessed with: (g/kg/day)	CRITICAL	⨁◯◯◯ Very low
Faltering growth / body composition: RCT: Growth in head circumference assessed with: (cm/week)	CRITICAL	⨁⨁◯◯ Low
Faltering growth / body composition: RCT: Head circumference Day 21 (cm) assessed with: (cm)	CRITICAL	⨁⨁◯◯ Low
Duration of hospital stay - not reported	IMPORTANT	-
Time to reach full enteral feeds	IMPORTANT	⨁⨁◯◯ Low
Bronchopulmonary dysplasia	IMPORTANT	⨁◯◯◯ Very low
Confirmed and suspected sepsis: RCT	IMPORTANT	⨁◯◯◯ Very low
Retinopathy of prematurity: RCT	IMPORTANT	⨁◯◯◯ Very low
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	Possibly important uncertainty about or variability in how much people value the main outcomes? **Values for Māori** No additional evidence available.	

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	**Human-based fortifier versus bovine-based fortifier for preterm infants - moderate certainty evidence** Uncertain effect on mortality, NEC (≥ stage 2) **Human-based fortifier versus bovine-based fortifier for preterm infants - low certainty evidence** Uncertain effect on surgical NEC, length increment, head circumference growth and head circumference at day 21, time to reach full enteral feeds **Human-based fortifier versus bovine-based fortifier for preterm infants - very low certainty evidence** Uncertain effect on neurodevelopmental impairment, feeding interruptions, fully breastmilk feeding at discharge, rate of weight gain, length and weight at day 21, bronchopulmonary dysplasia, sepsis and retinopathy of prematurity **Balance of effect 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	**Human-milk-derived breastmilk fortifier cost** Cost for one day per infant at 180 mL/kg/day is approximately $535 to $803 per day. If used for ELBW infants (birthweight <1000 g) and continued until 34 weeks CGA (~10 weeks = 70 days), the cost would be **$37,450 to $56,175 per baby per admission.** **Bovine-derived breastmilk fortifier cost** Cost for one day per infant at 180 mL/kg/day is approximately $5.80 to $9 per day. If used for ELBW infants (birthweight <1000 g) and continued until 34 wks CGA (~10 weeks = 70 days), the cost would be **$406 to $630 per baby (for 70 days) per admission** **Cost difference is** approximately $37,044 to $55,545 per infant per admission. (Large). **Resources required for Māori** No additional evidence available.	Cost estimates were based on the cost of a human milk-derived fortifier that is available now in Australia and used in ELBW infants until they are 34 weeks corrected age. Moderately certain.

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	The exact cost of using human milk-based fortifier in Aotearoa New Zealand is unknown but is unlikely to be less than what Australian hospitals pay. The exact cost of using bovine-based fortifier is certain.	

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	There are no studies that assess the specific cost-effectiveness of human-based fortifier compared with bovine-based fortifier, particularly in the context of preterm infants.	

the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	Cost-effectiveness would need to be assessed in the New Zealand setting, rather than relying solely on international data. This is because the background rate of breastmilk feeding and NEC are critical for a proper cost-benefit analysis. **Cost effectiveness for Māori** 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** Pēpi Māori experience higher rates of preterm birth and associated complications, including NEC, which disproportionately impacts whānau Māori due to systemic inequities in healthcare access and outcomes. The high cost of human-milk-derived fortifiers may create barriers to equitable access, exacerbating existing disparities in neonatal care. Furthermore, Māori perspectives on the use and commercialisation of human milk may differ from Western biomedical models, necessitating culturally appropriate consultation and decision-making. Ensuring Pēpi Māori receive optimal nutrition requires addressing affordability, accessibility and culturally safe healthcare policies that align with Te Tiriti o Waitangi obligations and Māori health aspirations. **Equity for Pacific families** Pacific infants also face a higher burden of preterm birth and associated complications, including NEC, which may be worsened by limited access to human milk-derived fortifiers due to financial and systemic barriers. Pacific communities often experience socioeconomic disadvantage, which can restrict access to expensive neonatal nutritional interventions, potentially leading to poorer health outcomes. Equity requires open discussion about the origin and purpose of fortifiers, respecting Pacific perspectives on shared nourishment and care. **Equity for underrepresented groups** Families from migrant or refugee backgrounds may be unfamiliar with human or animal-derived fortifiers and may have religious or cultural concerns. Without clear information in their preferred language, trust and consent may be affected. Equity demands culturally	

	appropriate education that supports informed decisions and aligns with families' values and beliefs.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Already standard practice in some USA and Australian hospitals. May not be ethically justifiable for some, depending on the source of breastmilk used for human milk fortifier.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	It is being used in more than one Australian NICU.	Probably not feasible due to the cost (especially in the current health environment)

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**	Probably no important uncertainty or	No important uncertainty or			

	JUDGEMENT						
		variability	variability	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
○	●	○	○	○

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