A whole population cohort analysis of survival to 34 weeks postmenstrual age without surgery for necrotising enterocolitis in very preterm infants receiving either pasteurised human donor milk or preterm formula as a supplement to their own mother's milk

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Brief title: Outcomes in very preterm infants receiving supplemental pasteurised human donor milk or preterm formula

Abstract

Background: Mothers of very preterm babies are able to provide about half the milk required for their baby during neonatal care. Preterm formula and pasteurised human donor milk (pHDM) are supplementary options, but which is optimal is unknown. We are planning a randomised, controlled, precision medicine platform trial to address this and other practice uncertainties.

Methods: To inform the trial design, w**e** performed a retrospective, exploratory analysis of babies born below 32 weeks gestation and admitted to neonatal units in England and Wales between 01-06-2017 and 31-05-2022. We utilised data from the National Neonatal Research Database that contains quality-assured clinical information sourced from Electronic Patient Records. We calculated the adjusted risk difference (ARD) for the primary (*survival to 34 weeks postmenstrual age (PMA) without surgery for necrotising enterocolitis)* and other outcomes for babies receiving only their own mother's milk and pHDM, and babies receiving only their own mother's milk and preterm formula. We estimated the relationship between exposure and outcome using a data-adaptive Super Learner approach with targeted maximum likelihood estimation.

Results: The primary (ARD -9·8%, 95%CI -11·4 to -8·2), and other outcome rates were lower in infants receiving pHDM supplementation (survival to 34 weeks PMA -10·7%, -12·2 to -9·1; necrotising enterocolitis surgery to 34 weeks PMA -0·6%, -1·3 to 0·03; treated retinopathy of prematurity -2·8%, -3·4 to -2·3; bronchopulmonary dysplasia -12·1%, -14·0 to -10·1); all-cause (10·7%, 9·1 to 12·2) and NEC-related mortality (1·0%, 0·4 to 1·5) were higher.

Conclusions: Our findings question the widely held view that pHDM is superior to formula as a supplement to own mother's milk. We adjusted for factors that influence the risk of necrotising enterocolitis and death but cannot exclude the possibility of confounding. Our data provide compelling justification for a randomised controlled trial to resolve this important clinical care uncertainty.

What is already known on this topic

- Randomised controlled trial evidence to-date indicates uncertainty around the efficacy of supplemental pasteurised human donor milk to improve outcomes
- A fear is that exposure to formula made from cow-milk might increase the risk of necrotising enterocolitis; a hope is that despite pasteurisation, human donor milk might retain non-nutritive factors protective against necrotising enterocolitis
- The longstanding global uncertainty around the optimal feed supplement for insufficient maternal milk following very preterm birth has led to polarised clinical opinion, confusion among staff, anxiety for parents and families, and a perpetuation of non-evidenced care

What this study adds

- This whole population study, adjusting for known confounders, identifies reduced likelihood of survival to 34 weeks postmenstrual age without surgery for necrotising enterocolitis, in very preterm babies fed a sole diet of human milk (own mother's milk and pasteurised human donor milk) compared with those receiving own mother's milk supplemented with preterm formula
- The risk difference in the likelihood of survival to 34 weeks postmenstrual age without surgery for necrotising enterocolitis is inversely related to gestational age
- This study also raises the possibility of competing outcomes as babies receiving a sole diet of human milk (own mother's milk and pasteurised human donor milk) had lower rates of treated retinopathy of prematurity and bronchopulmonary dysplasia

How this study might affect research, practice, or policy

- This study provides compelling justification to obtain high-quality randomised controlled trial evidence to determine the optimal supplement for very preterm infants when there is insufficient own mother's milk

Introduction

Maternal milk is the bedrock of newborn nutrition and uniquely also provides multiple non-nutritive benefits through biologically active molecules with anti-infective, immune-modulating, endocrine and growth-promoting properties. These non-nutritive components are of particular importance to infants born very preterm who are at high-risk of a range of serious morbidities. Very preterm infants (born below 32 weeks gestation) initially receive feeds by orogastric or nasogastric tube as co-ordinated sucking and swallowing is a developmental milestone that is not reached until around 34 weeks post-menstrual age. Hence, mothers who deliver very preterm need to express milk for several weeks. They widely report this as stressful and difficult. [1, 2]

On average, mothers of very preterm babies are only able to provide about 50% of the milk volume to meet their baby's needs. [3] Options to make up the shortfall are cow-milk-based formula or pasteurised human donor milk (pHDM). The manufacture of formula is highly quality controlled, and products designed to meet the needs of the very preterm infant are available. Formula has consistent composition and energy density, but uncertain and at best limited non-nutritive efficacy. Many practitioners fear that exposure to cow milk products increases the risk of the serious acquired gastrointestinal inflammatory condition, necrotising enterocolitis (NEC) that often requires surgical intervention and can be fatal. Human donor milk has low and highly variable nutrient density and requires pasteurisation to prevent transmission of infectious agents. Pasteurisation inactivates or reduces non-nutrient biologically active components hence the extent of non-nutritive benefit is also uncertain.

The most recent Cochrane Library review [4] identifies only five trials comparing feeding with pHDM versus formula as a supplement to own mothers milk. [5-9] The accompanying meta-analysis shows no statistically significant differences in NEC, all-cause mortality), invasive infection, or in the single trial examining this outcome, neurodevelopment at 18 months. [4]

As part of the development of a neonatal, precision-medicine platform trial to evaluate the efficacy of multiple interventions, including pHDM, to prevent or treat NEC, we conducted an exploratory analysis of population-based observational data.

Methods

We performed an exploratory, retrospective cohort analysis of all babies born below 32 weeks gestation and admitted to a neonatal unit in England and Wales between 1st June 2017 and 31st May 2022. The analysis was conducted under UK Health Research Authority Research Ethics Committee approval reference 21/LO/0024. We utilised data from the National Neonatal Research Database curated for data science applications (NNRD-AI). The NNRD is a National Information Asset containing a standard data extract (the Neonatal Data Set, an NHS Information Standard; DAPB1595) from the Electronic Patient Records of all admissions to National Health Service (NHS) neonatal units. The NNRD is discoverable through the Health Data Research UK Alliance Gateway to external researchers seeking to request access. Data in the NNRD comprise detailed, de-identified demographic, daily, episodic, diagnostic and

outcome variables. Data are quality-assured prior to inclusion in the NNRD. In England and Wales neonatal care for extremely and most very preterm infants is not provided outside the NHS, hence the NNRD contains near-complete population data for these groups of infants. NNRD data are high quality as shown by less than 5% discordance with equivalent items collected independently for a trial performed to Good Clinical Practice standards. [10]

Statistical analysis

We calculated the adjusted risk difference (ARD) for outcomes in babies receiving only Own Mother's Milk and pHDM (without fortification; i.e. an exclusive human milk diet) to discharge, and babies receiving only Own Mother's Milk and Formula. The primary outcome was "*survival to 34 weeks* postmenstrual age (*PMA) without surgery for NEC*". Other outcomes were late onset bloodstream infection defined as a positive pure growth blood culture 72 hours or more after birth; bronchopulmonary dysplasia (BPD) defined as any respiratory support at 36 weeks PMA; treated retinopathy of prematurity (ROP); survival to 34 weeks PMA; survival to discharge; all-cause mortality to discharge; NEC surgery; and NEC-related mortality. We estimated the relationship between exposure and outcome using an automated data-adaptive Super Learner approach with targeted maximum likelihood estimation (TMLE), which is a doubly robust, maximum likelihood-based method for parameter estimation. [11-13] We adjusted the relationship for infant sex, gestational age, multiple birth, birth weight z score, and antenatal steroid exposure. We also adjusted for the additional variables Apgar scores at 1, 5, 10 min; intubation at delivery; drugs administered at delivery; cardiac compressions during resuscitation; surfactant given during resuscitation; and surfactant, inotropes, insulin and invasive ventilation on day 1. We used the cross-validated TMLE [14] to estimate the prediction of outcomes and exposures. This included a predefined library of algorithms, each fitted over a grid of hyperparameters incorporating the ensemble Super Learner. [15, 16] This library included extreme gradient boosting with 200, 500, and 1,000 trees, maximum tree depth of 4, 5, or 6, and shrinkage parameters of 0.01, 0.001, or 0·0001, random forests with minimum node sizes of 10, 500, and 2500 trees, 2, 3, and 4 predictor variables chosen at random for each split, and sampling with and without replacement. We fitted least absolute shrinkage and selection operator (LASSO) and elastic-net regularised generalised linear models with elastic net mixing parameter = 0.0 (ridge penalty), 0·2, 0·4, 0·6, 0·8, or 1·0 (LASSO penalty) as well as generalized linear models and the simple mean. We used 10-fold cross validation to fit each ensemble learner and the binomial loss function to improve Super Learner. To avoid the need for empirical process conditions, we gave the TMLE algorithm an additional layer of 10-fold cross-validation (also known as sample splitting or cross fitting). [17] .

From the original TMLE fit, we computed efficient influence function values for each infant, to estimate a function for the risk difference across gestational age categories. We calculated risk differences for each value of the effect-measure modifier using predictions from the fit of this model across the range of gestational age categories. We estimated uncertainty intervals by 100 iterations bootstrapping the second stage fit. We generated plots with

ggplot2 R package. We used multiple imputation to estimate missing values setting the number of imputations to 10. Depending on the variable type, we used linear or logistic regression to predict missing values. We used a sequential imputation with chained equations to impute s a multivariate model with 10 numbers of iteration for the burn-in period. We ran all analyses with and without imputation as a sensitivity analysis.

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Results

Over the period 1st June 2017 to 31st May 2022, neonatal units in England and Wales admitted 36058 infants below 32 weeks gestation. Of these, 1007 infants received only feeds of unfortified Own Mother's Milk and pHDM (exclusive human milk), and 7133 only feeds of Own Mother's Milk and Formula, to discharge (Table 1).

Figure 1 shows the proportion of infants in each cohort surviving to 34 weeks PMA without NEC surgery by week of gestational age at birth, adjusted for infant sex, gestational age, multiple birth, birth weight z score, and antenatal steroid exposure. This indicates that survival to 34 weeks PMA without NEC surgery is higher for infants receiving feeds of Own Mother's Milk and Formula and that the difference between the cohorts increases with decreasing gestational age. Figures 2a and 2b show the adjusted proportions in each cohort surviving to 34 weeks PMA, and receiving NEC surgery to 34 weeks PMA. These figures indicate that the major difference between the cohorts occurs in relation to survival, with minimal difference in the rate of NEC surgery.

Table 2 shows survival to 34 weeks PMA without NEC surgery by birth gestational age, and the adjusted difference between the cohorts. Survival to 34 weeks PMA without NEC surgery was lower in babies receiving feeds of Own Mother's Milk and pHDM (overall ARD -9·8%, 95% CI -11·4 to -8·2). The difference increased with decreasing birth gestational age with the widest difference in babies born at 24 weeks gestation (ARD -51·5%, 95%CI -58·8 to -44·3).

Table 3 shows unadjusted and adjusted outcomes. In unadjusted analyses, babies receiving exclusive human milk feeds had significantly lower survival to 34 weeks PMA without NEC surgery, lower survival to 34w PMA, a higher rate of NEC surgery to 34w PMA, lower treated ROP and BPD, higher late onset bloodstream infection, higher NEC-related mortality and higher all-cause mortality to discharge. Following adjustment, the lower survival to 34 weeks PMA without NEC surgery (ARD -9·8%, -11·4 to -8·2), survival to 34w PMA (ARD -10·6, -12·1 to -9·1), treated ROP (ARD -2·8%, -3·4 to -2·3), and BPD (ARD -12·1%, -14·0 to -10·1), and higher NEC-related (ARD 1·0%, 0·4 to 1·5) and all-cause mortality (ARD 10·7, 9·1 to 12·2) remained statistically significant.

The lower likelihood of survival to 34 weeks PMA without NEC surgery and survival to 34 weeks PMA was also evident in the analysis additionally adjusting for markers of early illness severity (Supplemental Table S1). Multiple logistic regression also identified a highly significant reduction in the odds of survival to 34 weeks PMA without NEC surgery (Supplemental Table S2) in babies receiving exclusive human milk feeds.

Discussion

Contrary to widely held belief, the chance of survival without requiring surgical treatment for NEC is lower in babies born very preterm who receive an exclusive human milk diet compared with those fed Own Mother's Milk supplemented with Formula. The difference appears driven by lower survival, with no convincing difference in the rate of surgical NEC. Deaths attributable to NEC as well as all-cause mortality were also higher in the group receiving pHDM supplements. Conversely, in keeping with other studies, rates of treated ROP and BPD were lower in babies receiving an exclusive human milk diet, [18, 19] raising the possibility of competing risks. Our data are observational, may reflect residual confounding, and should not guide practice. However, they do indicate the need for randomised controlled trial evidence to resolve the uncertainty around the optimum milk supplement for very preterm babies.

A strength of our study is that we assessed the most severe form of NEC, namely that leading to need for surgery, or death, thus minimising any effect of ascertainment bias. This is an important consideration as NEC has a broad spectrum of severity, and the diagnosis of milder cases involves considerable subjectivity. We adjusted for gestational age, birthweight z score, sex, multiple birth, and antenatal steroid exposure as these are major factors influencing mortality and susceptibility to NEC. We additionally adjusted for variables indicative of greater illness severity, as these are also associated with greater NEC risk. However, we acknowledge that adjustment for known confounders may have been insufficient to capture differences in illness severity fully. Clinicians may preferentially choose to use pHDM when they are particularly concerned about an infant's wellbeing and hence this decision may be biased towards the most unwell and least likely to survive. Of note, the magnitude of the difference in survival to 34 weeks PMA without NEC surgery increased with greater degree of immaturity, and birth weight z score was also highly statistically associated with the outcome indicating need to incorporate gestational age and degree of fetal growth restriction as precision medicine factors in randomised trials to identify optimum enteral feeding practice.

Other reasons why supplementation with pHDM might lead to lower survival warrant consideration. If pHDM is considered equivalent to Own Mother's Milk and provides a sense of security, this might adversely affect a mother's motivation to express, and the support provided by clinical staff to encourage her to do so, which might result in reduced receipt of own mother's colostrum and breast milk. Thus, Hard et al describe a fall in the proportion of extremely preterm infants in Sweden exclusively receiving maternal milk at discharge from 55% in 2004 to 16% in 2013, concurrent with a policy of feeding pHDM until around 34 weeks

PMA to supplement mother's milk.[20] Colostrum is rich in bioactive substances and prebiotic oligosaccharides. Not receiving these protective components might reduce an infant's resistance to bloodstream infection and NEC. Evolutionary science suggests that human milk evolved primarily to serve an anti-infective, not nutritional, purpose [21] but pasteurisation destroys or substantially reduces non-nutritional biological components. [22] Hence, pHDM is not equivalent to milk from a baby's own mother. Additionally, milk composition varies between mothers, with many anti-infective and immunological properties uniquely tuned to a specific mother-infant dyad. [23] Human milk also has a dose response effect [24] but we were unable to evaluate feed volumes, as these data are not routinely entered into Electronic Patient Record systems and hence not available in the NNRD.

There is wide variation in practice in relation to the use of pHDM. [25, 26] Neither the presence of a milk bank nor patient characteristics fully explain this variation indicating high likelihood of clinician uncertainty as the explanation. [27] On average, less than a third of infants born below 32 weeks' gestation in the UK receive any pHDM during their neonatal unit stay. [28] The hope is that despite pasteurisation Human Donor Milk retains some beneficial non-nutritive biological properties. It is also possible that avoidance of cow milk products, rather than a direct protective effect, mediates any benefits. However, despite advocacy for human milk banks, and the emergence of a for-profit human milk industry, there is a continuing lack of robust evidence of short and long-term benefits, and safety. Only five trials to-date have compared feeding with pHDM versus formula as a supplement to Own Mother's Milk. [5-9] They show no significant differences in NEC, all-cause mortality, invasive infection, or neurodevelopment. However, of most concern is the possibility of harm from the use of pHDM during the third trimester, a particularly crucial period for brain growth and development. Donor milk has low nutrient density and studies including Cochrane Library meta-analyses [4] consistently show slower growth with pHDM, even when nutrient enriched. O'Connor et al [8] compared development at 18 months' corrected age in very low-birth-weight infants randomised to receive pHDM or Preterm Formula as a supplement to Own Mother's Milk. More children in the pHDM group had cognitive composite scores indicative of neuro-impairment compared with the formula group (27·2% vs 16·2%; ARD 10·6%; 95% CI 1·5% to 19·6%; *P* = 0·02). The pHDM group also had a worse mortality and morbidity index, and lower neurodevelopment scores though the differences were not statistically significant. Our analysis adds to the need to consider the possibility of harm arising through supplementation with pHDM.

The current Cochrane meta-analysis of data from nine trials comparing pHDM and formula as both sole diet or supplement shows a higher risk of NEC in the formula-fed group (RR 1·87; 95% CI 1·23 to 2·85) and is often cited as justification for widespread adoption of donor milk (4). However, there are important caveats. Four of the nine trials were conducted in the 1980s when the patient population differed substantially from that of today. There were only 1675 infants in total across all studies, which is an inadequate information size; study methodological quality was poor; and medically managed NEC was included in the outcome,

which is an imprecise diagnosis highly open to ascertainment bias. There were no significant differences in outcomes that would have provided important corroboratory evidence of benefit from pHDM (all-cause mortality, invasive infection and days after birth to establish full enteral feeding), or in neurodevelopment. Evidence that the use of pHDM helps establish enteral feeding or lactation is also uncertain. A systematic review and meta-analysis showed no difference in exclusive breastfeeding at hospital discharge in very preterm infants after the introduction of pHDM and noted that in certain settings, rates might decrease. [29]

In 2014, the James Lind Alliance Preterm Birth Priority Setting Partnership involving parents, the public and clinicians ranked "*Which interventions are most effective to prevent NEC in premature babies?*" and "*What is the optimum milk feeding regimen for preterm infants including use of donor and formula milks*?" 2nd and 6th among the top ten research questions. [30] Our study forms part of preparatory work over several years, to develop a randomised comparison of pHDM and Preterm Formula as supplements for insufficient Own Mother's Milk. We have held UK focus groups with parents and former patients, to obtain views on study designs and co-designed an initial draft "Participant Information Sheet". [2] With the help of the European Foundation for the Care of Newborn Infants, we held focus groups with parents across Europe. [31] We have also held webinars and focus groups with clinicians. We identified strong support for our planned study and that religious beliefs, cultural views, personal preferences, and information provided influence the acceptability of pHDM to parents. Paradoxically, many parents felt that clinician acknowledgement of the uncertainty around the optimum supplement and opportunity to resolve this by trial participation would help alleviate their anxiety. [2] Conversely, we identified anxiety and cognitive dissonance among some clinicians in which they recognised the uncertainties that justify a trial but felt unable to participate because of their strongly held views. [2]

The uncertainty around the optimum supplement when there is a shortfall in milk from a baby's own mother affects neonatal practice globally. The costs, production processes and quality standards for pHDM and Preterm Formula differ widely and are important considerations for healthcare systems. Despite the inadequate evidence base, some organisations recommend the use of pHDM over preterm Formula as a supplement for insufficient Own Mother's Milk. [32, 33] Neonatal medicine has adopted practices without good evidence many times previously. Placing infants prone [34] and the routine use of 100% oxygen during neonatal resuscitation [35] are examples of recommended practices subsequently found to be harmful when studied objectively. Where there is a lack of evidence, the recommendation that best benefits patients is to explain this with honesty and resolve the uncertainty through randomisation.

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Data sharing statement: The study data file and statistical code are available upon legitimate request; please contact author NM stating the purpose of the request.

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Table 1

Cohort characteristics

	Babies receiving Own Mother's Milk and pasteurised Human Donor Milk (N=1007)	Babies receiving Own Mother's Milk and Preterm Formula (N=7133)
Gestational Age, mean (weeks) ± SD	28·0±2·8	29·6±1·8
Missing	0	0
Boys (%)	558 (55·5)	3945 (55·3)
Missing	2	1
Birth weight z-score, mean ± SD	-0·3±0·9	-0·1±0·9
Missing	22	6
Multiple birth (%)	217 (21·5)	1749 (24·5)
Missing	0	0
Antenatal steroids (%)	932 (92·6)	6529 (91·8)
Missing	1	23
Apgar 1min, median (IQR)	6 (4-8)	7 (5-9)
Missing	121	906
Apgar 5min, median (IQR)	8 (7-9)	9 (8-9)
Missing	120	915
Apgar 10min, median (IQR)	9 (8-10)	9 (9-10)
Missing	280	2621
Intubation at resuscitation (%)	423 (42·0)	1908 (26·7)
Missing	0	0
Drugs administered at resuscitation (%)	44 (4.4)	204 (2.9)
Missing	0	0
Cardiac massage at resuscitation (%)	26 (2.6)	148 (2.1)
Missing	0	0
Surfactant at resuscitation (%)	423 (48·0)	1849 (25·9)
Missing	0	0
Surfactant on first postnatal day (%)	248 (24·6)	1617 (22·7)
Missing	0	0
Inotropes on first postnatal day (%)	90 (8·9)	319 (4·5)
Missing	0	0
Insulin given on first postnatal day (%)	13 (1·3)	36 (0·5)
Missing	0	0
Invasive respiratory support on first postnatal day (%)	411 (40·8)	2048 (28·7)
Missing	0	0

Table 2

Survival to 34 weeks postmenstrual age without NEC surgery (%) by gestational age at birth, and difference adjusted for gestational age, sex, multiple birth, birth weight z-score, and antenatal steroids (ARD); a negative difference means the outcome rate is lower in babies receiving pasteurised Human Donor Milk and Own Mother's Milk

Gestational age (weeks)	Pasteurised Human Donor Milk and Own Mother's Milk% (n=984)	Formula and Own Mother's Milk% (n=7104)	ARD% (95% CI)
23 (n=125)	10 (15·4)	40 (66·7)	-50.3 (-62·3 to -38·3)
24 (n=198)	15 (17·6)	78 (69·0)	-51·5 (-58·8 to -44·3)
25 (n=242)	22 (29·3)	138 (82·6)	-48·8 (-56·2 to -41·5)
26 (n=302)	30 (42.9)	215 (90·3)	-38·6 (-44·7 to -32·6)
27 (n=397)	39 (67·2)	318 (93·8)	-25·5 (-30·2 to -20·7)
28 (n=637)	62 (72·9)	538 (97·4)	-17·7 (-22·3 to -13·0)
29 (n=984)	104 (93·7)	854 (97·8)	-7·2 (-9·8 to -4·6)
30 (n=1912)	159 (95·2)	1735 (99·4)	-3·5 (-5.5 to -1·5)
31 (n=3285)	264 (98·5)	3006 (99·6)	-1·0 (-2·4 to 0·4)
Total	705 (71·6)	6922 (97·4)	-9.8 (-11·.4 to -8·2)

ARD: Adjusted Risk Difference

Table 3

Unadjusted and adjusted risk differences (adjusted for gestational age, sex, multiple birth, birth weight z-score, and antenatal steroids) in babies receiving feeds of Own Mother's Milk and pasteurised Human Donor Milk and Own Mother's Milk and Preterm Formula; a negative difference means the outcome rate is lower in babies receiving pasteurised Human Donor Milk and Own Mother's Milk

Outcomes	Pasteurised Human Donor Milk and Own Mother's Milk% (n=1007)	Formula and Own Mother's Milk% (n=7133)	URD% (95%CI)	ARD% (95%CI)
Survival to 34 weeks postmenstrual age without NEC surgery (%)	708 (70·3)	6949 (97·4)	-27·1 (-29·9 to -24·2)	-9·8 (-11·4 to -8·2)
Survival to 34 weeks postmenstrual age (%)	722 (72·0)	7051 (98·8)	-26·8 (-29·6 to -24·0)	-10·6 (-12·1 to -9·1)
NEC surgery to 34 weeks postmenstrual age (%)	36 (3·5)	122 (1·7)	1·8 (0·7 to 3·0)	-0·6 (-1·3 to 0·03)
Treated ROP (%)	8 (0·8)	163 (2·3)	-1·5 (-2·1 to -0·.8)	-2·8 (-3·4 to -2·3)
BPD (%)	134 (13·5)	1405 (19·9)	-6·4 (-8·7 to -4·1)	-12·1 (-14·0 to -10·1)
Late onset bloodstream infection (%)	82 (8·1)	218 (3·0)	5·1 (3·3 to 6·8)	0·4 (-0·6 to 0·01)
NEC-related mortality (%)	42 (4·1)	39 (0·5)	3·6 (2·4 to 4·9)	1·0 (0·4 to 1·5)
All-cause mortality to neonatal unit discharge (%)	294 (29·4)	137 (1·9)	27·5 (24·7 to 30·3)	10·7 (9·1 to 12·2)

URD: Unadjusted risk difference; ARD: Adjusted risk difference

Figure 1

Estimated chance of survival to 34 weeks postmenstrual age without necrotising enterocolitis surgery, by birth gestational age, for babies receiving feeds of Own Mother's Milk and pasteurised Human Donor Milk (blue line) and feeds of Own Mother's Milk and Formula (red line)

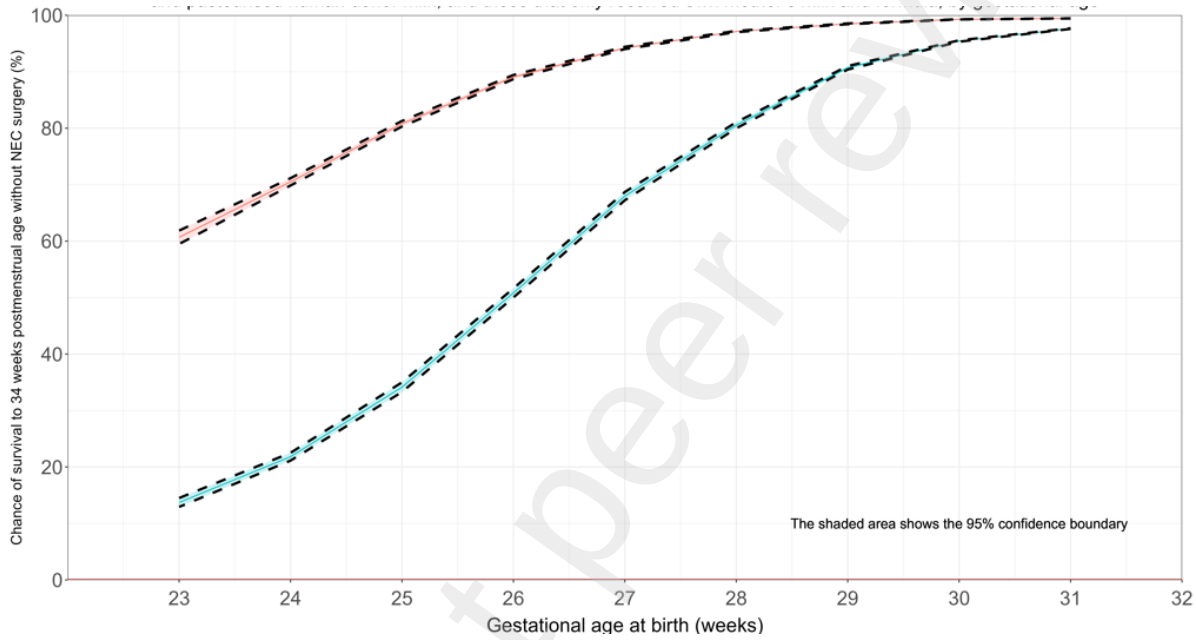


Figure 2a

Difference in the estimated chance of survival to 34 weeks postmenstrual age, by birth gestational age, for babies receiving feeds of Own Mother's Milk and pasteurised Human donor Milk and feeds of Own Mother's Milk and Formula; a negative difference indicates survival is lower with pasteurised Human Donor Milk supplementation

The shaded area shows the 95% confidence boundary (adjusted for infant sex, gestational age, multiple birth, birth weight z score, and antenatal steroid exposure)

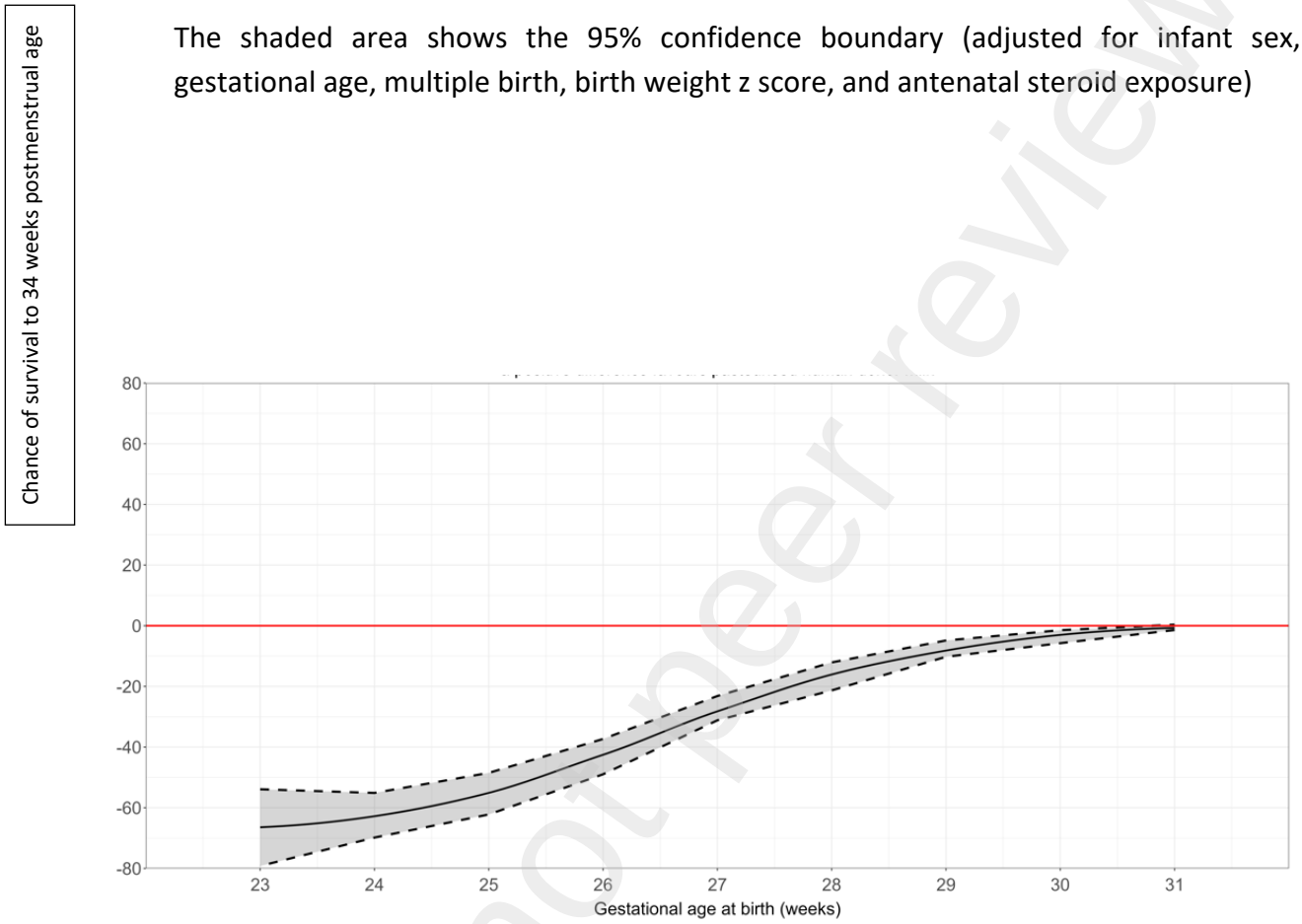
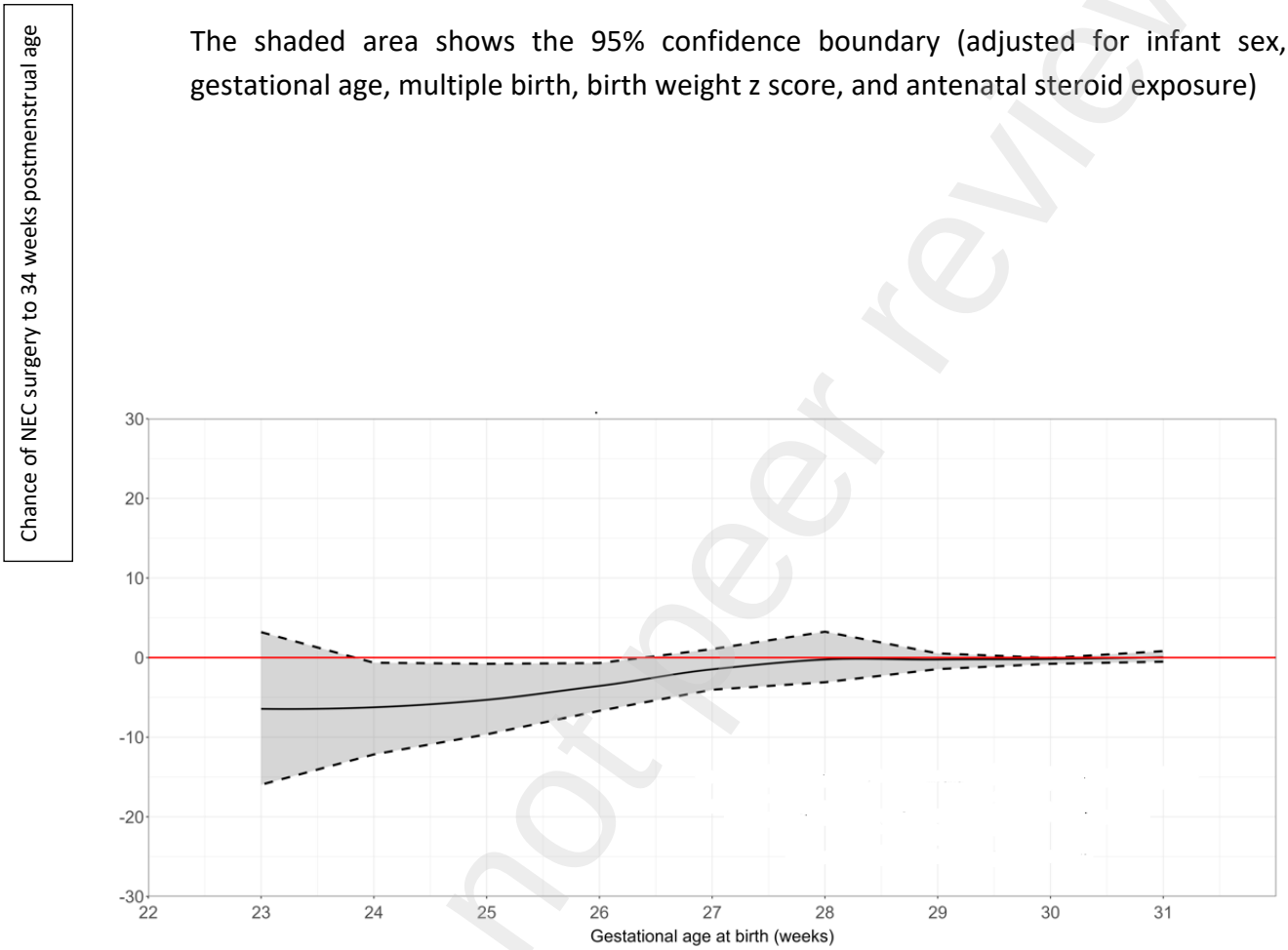


Fig 2b

Difference in the estimated chance of necrotising enterocolitis surgery to 34 weeks postmenstrual age, by birth gestational age, for babies receiving feeds of Own Mother's Milk and pasteurised Human Donor Milk and feeds of Own Mother's Milk and Formula; a negative difference indicates the chance of surgery is lower with pasteurised Human Donor Milk supplementation

The shaded area shows the 95% confidence boundary (adjusted for infant sex, gestational age, multiple birth, birth weight z score, and antenatal steroid exposure)



Supplementary Table S1

Adjusted risk differences in babies receiving feeds of Own Mother's Milk and pasteurised Human Donor Milk and Own Mother's Milk and Preterm Formula; a negative difference means the outcome rate is lower in babies receiving Own Mother's Milk and pasteurised Human Donor Milk

Outcomes	Pasteurised Human Donor Milk and Own Mother's Milk% (n=1007)	Formula and Own Mother's Milk% (n=7133)	ARD% (95%CI)
Survival to 34 weeks postmenstrual age without NEC surgery (%)	708 (70·3)	6949 (97·4)	-9·8 (-11·3 to -8·3)
Survival to 34 weeks postmenstrual age (%)	722 (72·0)	7051 (98·8)	-10·7 (-12·1 to -9·3)
NEC surgery to 34 weeks postmenstrual age (%)	36 (3·5)	122 (1·7)	-0·7 (-1·4 to -0·04)

ARD: Adjusted risk difference estimated by TMLE

Adjustment variables are gestational age, sex, multiple birth, birth weight z-score, antenatal steroids, Apgar score at 1, 5 and 10 min, intubation for resuscitation, any drugs at resuscitation, cardiac compression at resuscitation, any inotropes on day 1, any invasive ventilation on day 1, surfactant at resuscitation, insulin treatment on day 1, surfactant on day 1

Supplementary Table S2

Multiple logistic regression model based on two set of confounding variables (model 1 and model 2) assessing the association between intervention and survival to 34 weeks postmenstrual age without NEC surgery

	aOR1 (95% CI)	P value	aOR2 (95% CI)	P value
Intervention				
Formula	Ref		Ref	
Donor	0·11 (0·09 to 0·15)	<0·0001	0·10 (0·08 to 0·13)	<0·0001
Sex				
Female	Ref		Ref	
Male	0·81 (0·63 to 1·04)	0·10	0·81 (0·63 to 1·04)	0·10
Gestational weeks	1·97 (1·87 to 2·07)	<0·0001	1·77 (1·67 to 1·88)	<0·0001
Multiplicity				
Singleton	Ref		Ref	
multiple	1·06 (0·78 to 1·44)	0·70	1·03 (0·75 to 1·43)	0·83
Antenatal steroids				
No	Ref		Ref	
Yes	1·45 (0·94 to 2·23)	0·09	1·35 (0·87 to 2·10)	0·18
Birth weight z-score	1·58 (1·36 to 1·82)	<0·0001	1·56 (1·33 to 1·82)	<0·0001
Apgar at 1 min	-	-	1·23 (1·15 to 1·32)	<0·0001
Apgar at 5 min	-	-	0·99 (0·90 to 1·10)	0·96
Apgar at 10 min	-	-	0·99 (0·87 to 1·12)	0·87
Any drugs at resuscitation	-	-	0·97 (0·59 to 1·57)	0·89
Cardiac compressions at resuscitation	-	-	1·45 (0·87 to 2·43)	0·16
Any inotropes on day 1	-	-	0·63 (0·44 to 0·91)	0·01
Any invasive ventilation on day 1	-	-	0·78 (0·58 to 1·07)	0·12
Surfactant at resuscitation	-	-	0·99 (0·67 to 1·46)	0·96
Insulin treatment on day 1	-	-	1·38 (0·64 to 2·96)	0·41
Surfactant on day 1	-	-	1·02 (0·78 to 1·34)	0·88
intubation for resuscitation at birth	-	-	0·94 (0·61 to 1·44)	0·78

aOR: Adjusted Odds Ratio estimated by two different set of confounding variables