Prioritising allocation of donor human breast milk amongst very low birthweight infants in middle-income countries

Celia Taylor[1], Yaseen Joolay[2], Abigail Buckle[1] and Richard Lilford[1]

1. Division of Health Sciences, University of Warwick Medical School, UK
2. Groote Schuur Hospital/University of Cape Town.

Word count (abstract): 244

Word count (main text): 5,320

Number of references: 40

Number of tables: 3

Number of figures: 1

Acknowledgements: Dr Lloyd Tooke provided the clinical data required to build the model and his assistance is gratefully acknowledged.

Source of funding: CT and RL are funded by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care West Midlands initiative. This paper presents independent research and the views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of interest: The authors declare that they have no conflict of interest.

Contributor statement: RL conceived the study and advised on the design of the economic model. CT developed the economic model and drafted the manuscript. AB led the search for input values from the literature and YJ those from clinical practice. All authors revised and approved the final version of the manuscript.

ABSTRACT

The use of donor human breast milk instead of formula reduces the risk of necrotising enterocolitis (NEC) in preterm infants when their mother's own milk is insufficient. Use of donor milk is limited by the cost of establishing a milk bank and a lack of donors, but the optimal rationing of limited donor milk is unclear. This paper uses an economic model to explore how a limited donor milk supply should be allocated across very low birthweight infants in South Africa considering two outcomes: maximising lives saved and minimising costs.

We developed a probabilistic cohort Markov decision model with 10,000 infants across four birthweight groups. We evaluated allocation scenarios in which infants in each group could be exclusively formula-fed or fed donor milk for 14 or 28 days and thereafter formula until death or discharge.

Prioritising infants in the lowest birthweight groups would save the most lives, while prioritising infants in the highest birthweight groups would result in the highest cost savings. All allocation scenarios would be considered very cost-effective in South Africa compared to the use of formula; the 'worst case' was $619 per Disability Adjusted Life Year averted.

There is a compelling argument to increase the supply of donor milk in middle income countries. Our analysis could be extended by taking a longer-term perspective, using data from more than one country and exploring the use of donor milk as an adjunct to mother's own milk, rather than a pure substitute for it.

Key words: donor human breast milk, very low birthweight, necrotising enterocolitis, economic evaluation, rationing

INTRODUCTION

In the absence or limited supply of breastmilk from a preterm or very low birthweight (VLBW) infant's biological mother, leading health organisations recommend the use of donor human milk as the first alternative (Arslanoglu et al., 2013; Eidelman et al., 2012; UNICEF, 1995). This recommendation results from evidence that donor milk reduces the incidence and severity of necrotising entercolitis (NEC) (Arslanoglu et al., 2013; Quigley & McGuire, 2014). Given appropriate safeguards including the screening of potential donors (NICE, 2010), there are relatively few safety concerns regarding the use of donor milk and a recent systematic review did not find evidence that donor milk crowded out the provision of a mother's own milk (Williams, Nair, Simpson, & Embleton, 2016). However, although there are no definitive bottom-up costings of supplying donor milk, it is clearly more expensive than using formula when a mother's own milk is not available (Jegier, Meier, Engstrom, & McBride, 2010) and thus its cost-effectiveness needs to be considered when deciding whether – and if so, to whom - it should be provided. This is a key issue in low- and middle- income countries where resources for healthcare are particularly scarce (WHO Commission on Macroeconomics and Health, 2001).

A previous study examined the cost-effectiveness of donor milk as an *adjunct* to mother's own milk and alongside an intervention to increase breastfeeding rates (Renfrew et al., 2009). However a systematic review of the cost-effectiveness of exclusive donor milk feeding compared with *exclusive* formula milk feeding (Buckle & Taylor, 2017) identified only three studies in two papers offering any form of economic evaluation (Arnold, 2002; Wight, 2001). All of these were cost-minimisation analyses and, while all reported likely cost savings from the use of donor milk, none is sufficiently robust for decision-making. For example, all three studies assumed that donor milk would be as effective as mother's own milk in preventing NEC and none included the healthcare costs arising when an infant who would have died from NEC survives. None of the studies included a sensitivity analysis.

This lack of good quality specific evidence of cost-effectiveness limits attempts to increase the resources required to develop and run milk banks. Supply may also be limited by a lack of donors and hence there is often insufficient donor milk to meet demand (Medo, 2013; Miracle, Szucs, Torke, & Helft, 2011; Tully, 2002). Where there is excess demand, it is necessary to prioritise allocation. The prioritisation criteria promoted by the Human Milk Banking Association of North America incorporate recipient factors, maternal factors and time factors, affording the highest priority to preterm infants (Tully, 2002). The criteria are viewed as a means of promoting an ethical approach to allocation (Miracle et al., 2011; Tully, 2002), but are not based on a formal analysis of costs versus benefits (British Association of Perinatal Medicine, 2015). Moreover, they do not explicate how decisions should be made *within* specific groups so it is not surprising that both UK and US surveys of neonatal units have found significant variation in the criteria applied in practice (Hagadorn, Brownell, Lussier, Parker, & Herson, 2016; Zipitis, Ward, & Bajaj, 2015).

This paper seeks to address the current lack of a full economic model and provide recommendations as to how donor milk should be allocated amongst VLBW infants according to birthweight. We consider the effect of different approaches to prioritisation on two NEC-related outcomes resulting from the use of donor milk as an alternative to formula: the number of lives saved and short-term costs/savings to the health service.

METHODS

This study follows the Consolidated Health Economic Evaluation Reporting Standards (Husereau et al., 2013).

Setting and location

The setting for the model is neonatal units in South Africa that need to decide how to allocate donor milk amongst VLBW infants (<1,500g). We selected a middle-income country focus because of the increased pressure on healthcare resources in comparison with high-income countries and better availability of data in comparison with low-income countries. Furthermore, most of the world's population lives in middle-income countries. We have used clinical data from Groote Schuur Hospital in Cape Town to help parameterise our model as outlined below. Groote Schuur is a state funded Level 3 hospital. The neonatal unit has 75 beds in total, and admits approximately 2,000 babies every year, 25% of whom have a birthweight ≤1500g. Approximately 10% of admissions are ELBW. The 20 bedded NICU is able to provide non-invasive and invasive ventilation including High Frequency Oscillation and Nitric Oxide as well as offer Therapeutic Hypothermia. The 55 remaining beds are high care and general neonatal beds.

Study perspective and duration

We adopted a health services perspective, including the costs of neonatal care up to the point of death or initial discharge (maximum 14 weeks). In the model, events occur at the end of each week, although milk volumes are calculated on a daily basis. Costs arising to parents and society and long-term health service costs are excluded. Costs are shown in 2015 US Dollars at Purchasing Power Parity (PPP), inflated to 2015 values using local indices and converted to PPP using the World Bank exchange rates for 2015 where required (World Bank, 2015b).

Target population and subgroups

The target population is VLBW infants (<1,500g), the target population for provision of donor milk in the preterm feeding policy for the Western Cape province of South Africa. In the model a cohort of 10,000 VLBW infants is considered, which represents around one-third of the annual number of VLBW infants across South Africa. VLBW is a proxy for preterm infants, since almost all data used to parameterise the model are from sources based on birthweight groups rather than gestational age. Four groups based on birthweight are used (500-750g, 751-1,000g, 1,001-1,250g and 1,251-1,500g), determined by the predominant stratification in the literature and based on 2012/13 Perinatal Problem Identification Program (PPIP) data aggregated across Western Cape and Mpumulanga (Pattinson & Rhoda, 2014). These data only present two VLBW categories, 500-999g and 1,000-1,499g, with 42.7% of VLBW infants in the 500-999g category and 57.3% in the 1,000-1,499g category. To provide the most realistic incrments between groups, we assumed that 46.4% of each category would be in the lower of our two groups and 53.6% in the upper (Table 1). The uncertainty in this distribution is considered in the probabilistic sensitivity analysis using a Dirichlet distribution (parameterised using the Pattinson & Rhoda data as described above) as recommended for multinomial data (Briggs et al., 2006) because the proportion in each group affects the volume of donor milk required for each allocation scenario.

Comparators

The study considers VLBW infants for whom no maternal milk can be provided (e.g. through maternal death, absence or specific contraindications). Such infants can be provided with either donor milk (intervention) or formula milk (control). Neither type of milk is fortified (a recent review did not find a statistically significant effect of fortification on outcomes (Brown, Embleton, Harding, & McGuire, 2016)) and no probiotics are added. Although non-maternal milk is often used as an adjunct to support mothers while their own milk supply is being established (British Association of Perinatal Medicine, 2015), we considered only donor or formula milk for the model given the lack of evidence on the effectiveness of mixed feeding on reducing the risk of NEC.

Time horizon – duration of donor milk feeding

For the lowest three birthweight groups (<1,251g), exclusive donor milk could be given for either 14 or 28 days (or until diagnosis of NEC or death, whichever comes soonest). However, the highest birthweight group (1,251-1,500g), exclusive donor milk could be given for 14 days or until diagnosis of NEC or death. These two time periods are often cited as critical for NEC risk (British Association of Perinatal Medicine, 2015; Yee et al., 2012). However, for the highest birthweight group, 14 days was used as the only option since an infant in this group surviving NEC-free would be expected to be discharged at 21 days. For the period following diagnosis of NEC or after 14/28 days, the infant would be given exclusive formula milk until death or discharge. Although donor milk may be used in practice to support the gut following diagnosis of NEC (British Association of Perinatal Medicine, 2015), we did not consider this here as our outcome measures only include the incidence and severity of NEC.

Donor milk allocation scenarios considered

Given the four birthweight groups and three durations of donor milk feeding as described above, there are 53 possible donor milk allocation scenarios, as listed in Appendix table 1. These scenarios have been split into eight donor milk availability groups according to the total volume of donor milk required per 10,000 VLBW infants: <5,000L, <10,000L, <15,000L, <20,000L, <25,000L, <30,000L, <35,000L and ≥35,000L.

Choice of health outcomes

The only condition included in the model is NEC, due to the lack of evidence regarding the effect of donor milk on other outcomes (Arslanoglu et al., 2013). Donor milk has been shown to reduce the risk of NEC (Quigley & McGuire, 2014) and breast milk has been shown to reduce its severity (Guthrie et al., 2003). NEC generally has two severity categories: medical and surgical; infants requiring surgery are generally sicker and have a poorer prognosis (Lin & Stoll, 2006). However for some infants (those with a particularly poor prognosis) only palliative care is provided. The effect of using donor milk rather than formula is estimated in terms of lives saved; the effect on morbidity of those who survive is excluded.

Risk of NEC with formula milk

Data from a large US-based retrospective cohort study (Fitzgibbons et al., 2009) are used to estimate the baseline risk of NEC in each birthweight group. The estimates are for all methods of feeding combined, so underestimate the risk for exclusive formula feeding, but we were unable to find a source that provided risks by birthweight and type of feeding. The risk for each group is included in the probabilistic sensitivity analysis (Table 1) using a Beta distribution as recommended for binomial data (Briggs et al., 2006), parameterised using the results of Fitzgibbons et al.'s study.

Measurement of effectiveness

The effect of donor milk feeding compared with formula feeding on the incidence of NEC (relative risk 0.36, 95% CI 0.18 to 0.71) is taken from the Cochrane Review by Quigley and McGuire (Quigley & McGuire, 2014). The estimate of the effect of receiving breast milk on the risk of surgical NEC (as opposed to medical NEC) is taken from a retrospective cohort study in the US reported by Guthrie and colleagues (Guthrie et al., 2003). The odds ratio reported in the paper (0.60, 95% CI 0.40 to 1.00) was converted into a relative risk using the method of Grant (Grant, 2014). Both of these relative risks and the uncertainty with which they are estimated by Quigley & McGuire and by Guthrie et al. are included in the probabilistic sensitivity analysis using log normal distributions, as recommended by Briggs et al., 2006. Where an infant was 'saved' from surgical NEC through the use of donor milk, they were assumed to receive medical management and survive. Given the absence of emprical evidence, we assume the effect of donor milk on both the risk and severity of NEC is the same regardless of birthweight.

NEC timing, severity and mortality by birthweight group

The distribution of timing of onset of NEC, severity and mortality of NEC cases is shown by birthweight group in Appendix table 2. These values are based on a review of NEC cases at the Groote Schuur Hospital and published evidence from Canada of an inverse relationship between birthweight and timing of onset (Yee et al., 2012). We assume that the severity and mortality of NEC cases is independent of the timing of onset. Where donor milk is given for 14 days, we assume that the risk and severity of NEC up until that point would be reduced, but that there would be no enduring effect of donor milk once it is replaced with formula.

Non-NEC mortality

Using neonatal mortality data from the Groote Schuur Hospital, we assume that a proportion of infants in each birthweight group die from other causes at the end of the first week of life (Table 1). Until the point of non-NEC mortality, all infants are cared for in the neonatal intensive care unit (NICU).

Milk volume

Feeding volumes are estimated based on the mean birthweight of an infant in each of the four birthweight groups. The means are estimated using a right-angled triangular distribution for each birthweight group (Table 1). Our approach to calculating milk volume is based on the policy implented at Groote Schuur Hospital as follows:

- Enteral feeding begins on day 1 and progresses as shown in Appendix table 3 until infants are receiving 216 ml/kg/day (based on the findings in the Cochrane Review by Morgan and colleagues (Morgan, Young, & McGuire, 2015)), regardless of type of milk received.
- Infants lose 10% of their birthweight in week 1, which is regained by the end of week 2.
- Subsequent weight gain occurs at the rate of 14g/kg/day, based on South African data (Lango, Horn, & Harrison, 2013), regardless of type of milk received.
- Infants stop receiving milk on diagnosis of NEC and are intially fed parenterally. Enteral feeding (using formula) resumes seven days after onset for those who survive medical NEC and 21 days after onset for those who survive surgical NEC, assuming, in the absence of empirical evidence, NEC does not influence infant weight. Infants with palliative NEC are fed parenterally for two days before death.

The volume of milk required varies by birthweight group, incidence and type of NEC and by timing of onset of NEC (Appendix table 4).

Milk costs

We use costs of USD 0.0529/ml for formula milk and USD 0.1371/ml for donor milk. The cost of formula milk was provided through personal communication with the Chief Dietician at RK Khan Hospital in KwaZulu Natal, South Africa based on ready-to-feed bottles of Similac Special Care (ZAR 68.9 for 236ml in 2015). We did not adjust for any wastage if not all of a bottle was used. The cost of donor milk was provided through personal communication with the Milk Matters milk bank in Cape Town, South Africa (ZAR 75.7 for 100ml in 2015). Donors are not paid for their milk. Our systematic review (Buckle & Taylor, 2017) has found eight estimates of the cost of donor milk, all from high-income countries. The lowest costs were from Scandinavia (USD 0.08-0.10/ml); costs from US sources ranged from USD 0.11 to 0.15/ml; and the highest costs were from the UK (USD 0.21 to 0.51/ml, all at 2015 PPP). However there was variation as to what cost components were included in these estimates making direct comparisons unreliable.

Length of stay

Appendix table 5 shows the number of days in each type of neonatal care (NICU, High care and Normal care) required by outcome and birthweight group, based on clinical data from Groote Schuur

Hospital. The total length of stay for infants acquiring NEC but not surviving varies according to the timing of onset of NEC (as shown in Appendix table 6).

Daily cost of care

As direct estimates of daily care costs were not available for South Africa (only charges billed to parents/insurers), we use two approaches to costing (Table 1):

- UK costs for each type of neonatal care are taken from the Department of Health's 2014 schedule of reference costs (Department of Health, 2014), which include the time of all healthcare and other staff and any medicines required. 2014 values were increased by 1% to adjust for inflation to 2015 values, as recommended (PSSRU, 2014) given the unavailability of 2015 values at the time of analysis.
- UK costs are adjusted to reflect the relative cost of care in South Africa based on data from the 2015 Comparative Price Report produced by the International Federation of Health Plans (International Federation of Health Plans, 2015). The (private healthcare) costs of ten different procedures in both the UK and South Africa were included in this report, with a mean costs ratio of 0.485 (i.e. costs in South Africa are 48.5% of those in the UK).

Other health service resource use and costs

Infants with surgical NEC require neonatal surgery for their condition. Based on clinical input from Groote Schuur Hospital, infants who die are assumed to have one operation and those who survive have three. The costs of these procedures are estimated using the same two approaches as for the daily cost of care (Table 1), based on UK reference costs for a major neonatal diagnosis, non-elective inpatients, short stay as used in a previous study (Renfrew et al., 2009). Many infants in South Africa receive neonatal care at a hospital which cannot provide such surgery, so we assume, based on local clinical advice, return ambulance transfers are required for 80% of infants, at standard South African rates (Republic of South Africa, 2016). Finally, all infants acquiring NEC require parenteral nutrition while in the neonatal intensive care unit. Fixed and daily costs of parenteral nutrition were obtained from Groote Schuur Hospital (Table 1).

Incremental cost of treating NEC

The estimated incremental cost of treating NEC (including parenteral nutrition but excluding milk costs) per infant is shown in Appendix table 6 by type of NEC, birthweight group and timing of onset. The comparator is infants who do not acquire NEC and who survive until discharge. For those who survive NEC, our estimates of the mean incremental cost of initial hospital treatment per infant are USD 26,000 for medical NEC and 67,500 for surgical NEC (2015 values at PPP).

Discount rate

As the maximum length of stay considered in the model is 98 days, no discounting of costs is required. The primary health outcome considered is lives saved which does not require discounting.

Choice of model

We developed a cohort simulation model with each cohort including 10,000 VLBW infants who cannot receive any of their own mother's milk. An example of the corresponding decision tree for the 1,251-,1500g birthweight group is shown in Figure 1. The model was developed using Excel 2010 and is available on request; a user can input their own unit costs and this will automatically change the results (keeping the clinical parameters constant). Using random draws from the relevant probability distributions, we simulated 1,000 cohorts to generate 95% credible intervals to reflect the uncertainty of the input parameters and repeated this process for both UK and South African cost estimates. The short-term nature of the model and its relative simplicity meant that a cohort simulation was preferred to a Markov model or an individual-level simulation.

Analytical methods

For each of the 53 donor milk allocation scenarios, we estimated the number of lives saved and incremental cost (or saving) associated with the use of donor milk in that scenario, compared to formula milk, using the mean values from the 1,000 simulated cohorts. Within each donor milk availability group, we identified the scenario that maximised the number of lives saved and minimised the incremental cost. We calculated the probability that these identified scenarios were optimal (i.e. the proportion of the 1,000 simulations in which that scenario maximised lives saved/minimised costs). For each allocation scenario, we also estimated the litres of donor milk needed to save one life and the net financial cost or saving associated with the use of one litre of donor milk. We estimated the cost-effectiveness of the use of donor milk in terms of the cost per Disability Adjusted Life Year (DALY) averted, valuing one neonatal life saved at 21.9 DALYs (Sabin et al., 2012). We started with the least cost-effective allocation scenario, comparing the cost per DALY averted with the WHO-CHOICE threshold of one GDP per capita (USD 13,165 in South Africa (World Bank, 2015a)) for a "very cost-effective" intervention (Tan-Torres Edejer, 2003).

Ethics

No primary data were collected for the purpose of conducting this study; thus although aggregated, anonymised data from Groote Schuur Hospital in Cape Town were used to provide some parameter values, ethical approval was considered not to be required.

RESULTS

Parameter values

Table 1 summarises the parameters included in the model as detailed in the methods section.

Maximising lives saved with a given availability of donor milk

Table 2 shows the optimal allocation of donor milk within each donor milk availability grouping in terms of maximising the number of lives saved per 10,000 VLBW infants. Apart from the <25,000L availability grouping, there is a high (>90%) probability that the scenario identified within each grouping is optimal. For the <25,000L availability grouping, a second allocation scenario was almost as effective. The two scenarios only differed by reallocating the 15-28 days of donor milk for the 751-1,000g birthweight group to 0-14 days for the 1,251-1,500g birthweight group, with the slightly less effective option just making it into the <25,000L availability grouping. When the supply of donor milk is limited, lives saved can be maximised by following two general rules: (1) prioritise infants in the two lowest birthweight groups (<1,000g) and (2) give donor milk for 14 days to two adjacent birthweight groups rather than for 28 days to only those in the lower of those two groups.

Minimising incremental costs with a given availability of donor milk

Table 3 shows the optimal allocation of donor milk within each donor milk availability group in terms of minimising the incremental costs to the health service per 10,000 VLBW infants, for UK and South African cost estimates. For both costing methods, the optimal allocation scenario with at least 5,000L of donor milk available is cost saving. With between 5,000 and 15,000L of donor milk, the optimal allocation scenario is to feed infants in the 1,001-1,250g birthweight group with donor milk for 14 days under both UK and South African costs. This remains the optimal allocation scenario using South African costs even when there is more than 15,000L of donor milk available per 10,000 VLBW infants. Under UK costs with more than 15,000L of donor milk available, the optimal allocation scenario is to give donor milk to all infants >1,000g for 14 days. As with maximising lives saved, there is a high probability that the scenario identified within each availability grouping is optimal (>80%).

Maximising the health returns to donor milk consumption

Across all levels of donor milk availability, the health returns associated with every 1L of donor milk are maximised when only infants in the 500-750g birthweight group are fed with donor milk for 14 days. In this scenario, a mean of 24 litres of donor milk is required to save one life (1L therefore saves 0.04 lives) and 48 infants need to be fed with donor milk in order to save one life.

Maximising the economic returns to donor milk consumption

With the exception of the <5,000L donor milk availability grouping, the economic returns (cost savings) associated with every 1L of donor milk are maximised when the 1,001-1,250g birthweight group are fed with donor milk for 14 days. In this scenario the net saving resulting from the use of every 1L of donor milk is USD 115 with UK costs or USD 25 with South African costs.

Making fair and efficient allocation decisions

In the worst-case allocation scenario in terms of cost-effectiveness (only giving donor milk to infants in the 500-750g birthweight group for 14 days), the incremental cost-effectiveness ratios were USD 619 per DALY averted using UK costs or USD 259 using South African costs. These ratios would be considered "very cost-effective" in South Africa based on the WHO-CHOICE threshold of one GDP per capita per DALY averted (Tan-Torres Edejer, 2003). Thus all other allocation scenarios would be "very cost-effective", with many of these cost saving and therefore dominating the use of formula milk. This suggests a clear case for the use of donor milk for all VLBW infants when their mother's milk is unavailable or insufficient to meet an infant's needs. However, insufficient supplies may mean that rationing is still required. Comparing the results in Tables 2 and 3 indicates that there is no optimum allocation scenario across both criteria (maximising lives saved and minimising costs) and therefore a subjective trade-off between saving lives and saving money would need to be made.

DISCUSSION

Summary of results

The results reported here suggest that the use of donor milk to reduce the incidence and severity of NEC in very low birthweight infants would be at least cost-effective, and most likely cost saving, in a middle-income country such as South Africa. Following the purchase of donor milk by a neonatal unit from a milk bank, the savings would be realised to the health service within a short time frame (i.e. during the infant's initial neonatal stay), although the provision of donor milk does require previous investment in the necessary infrastructure.

Our results suggest that health outcomes (measured in terms of lives saved) would be maximised by prioritising the lowest birthweight infants, but that cost savings would be maximised by prioritising those in the 1,000-1,250g and then the 1,251-1,500g birthweight groups. These apparently contradictory results are explained by differences in NEC rates between groups: NEC rates are highest in the lowest birthweight groups who therefore have the largest headroom for health gains; but where lives are saved, high healthcare "survivorship costs" ensue. Therefore those making allocation decisions may need to make a trade-off between saving lives and saving money.

Relationship to other studies

Our results confirm previous, but limited, economic evaluations undertaken for developed countries (Arnold, 2002; Wight, 2001) which also show that the exclusive use of donor milk can be cost-saving. Replicating economic evaluations in different international contexts is important as results may not be transferable (Boehler & Lord, 2016). We have not considered the ethics of rationing in any detail as others have done (Miracle et al., 2011; Tully, 2002) and some parents or guardians may object to the use of donor milk (British Association of Perinatal Medicine, 2015).

Strengths and weaknesses

We have been explicit about our assumptions, the sources of the data used as parameter values and incorporated uncertainty in a probabilistic sensitivity analysis, although not for all variables included. Nevertheless, assumptions are always open to criticism, although we reviewed all of these with a clinician to ensure that simplifying assumptions did not jeopardise the clinical validity of the model. We undertook a "back of the envelope" approach to identifying the potential impact of making significant changes to these assumptions but did not consider that any such changes would have signfiicantly changes our conclusions. Analysis of existing datasets, such as the UK's National Neonatal Research Database, would enable some of these assumptions to be tested, but testing others may require international collaboration on a prospective register of NEC patients.

We have also relied on existing datasets to parameterise our model, none of which are themselves perfect. For example, the parameter values identified from the literature are not all drawn from systematic reviews and, in the case of the effect of donor milk on the risk of requiring surgery for NEC, we have had to extrapolate from data for breast milk in general to donor milk, which may over-estimate the effectiveness of donor milk. Even though the estimate of the relative risk of NEC was taken from a systematic review, the authors of the review note weaknesses with the included studies and the lack of contemporary trials (Quigley & McGuire, 2014). For both these health outcomes, the 95% credible intervals from the cohort simulation were fairly wide, suggesting a need for further primary research to obtain a more precise estimate of the effect of using donor milk. In addition, we could not find any data for the effect of donor milk on the risk of NEC by birthweight so we had to assume the same relative risk across all groups.

Where we used data from South Africa, we relied on clinical data provided by one hospital and there may be variation across hospitals even within one country. Although published data for some parameters do exist for high income countries (most notably the US), for example the rate of surgical NEC (Hull et al., 2014), these data are not applicable to many middle-income settings due to the lack of specialist neonatal equipment such as ventilators. Our daily neonatal unit costs data were based on UK data because we were unable to obtain local costs data. Whilst data on South African charges could be obtained these were not considered a true reflection of the cost of care incurred by the health service and we therefore needed to estimate South African costs.

Our model has only considered the short-term effects of donor milk on one neonatal condition (NEC) and only from the perspective of the health service. We assumed donors are not paid for their milk; doing so would reduce the cost-effectiveness of donor milk relative to formula; and also that there was no wastage of milk. However, even with 25% wastage, total healthcare costs would increase by less than 1% and therefore incorporating wastage would not affect our conclusions. We did not include other conditions where donor milk may be beneficial due to a lack of evidence regarding the effect of donor milk (Meier, Patel, & Esquerra-Zwiers, 2017). However, survival following NEC may bring with it future health service costs and challenges for the survivor and their family, which may be particularly acute in low- and middle-income countries. We only included one criterion on which decisions regarding the allocation of donor milk could be made (birthweight), when in reality decisions may also be affected by maternal desire/intention to breastfeed and an infant's prognosis independent of birthweight. We only considered the use of donor milk as an exclusive substitute for formula milk when donor milk is often used to supplement a mother's own milk supply while it is being established (British Association of Perinatal Medicine, 2015). Research to evaluate the effectiveness of mixed feeding on NEC incidence is required, so this option could also be included in an economic evaluation.

Implications for practice

Given the promising cost-effectiveness of donor milk reported here, the allocation decisions assumed to be required in this paper should not have to be made, because sufficient donor milk

should be available for all VLBW infants when mother's own milk is not available. The need to allocate or ration donor milk should therefore be seen as a short-term problem, until the infrastructure required to ensure a plentiful, consistent and safe supply of donor milk to all neonatal units can be developed. Saying that such investment should be made because of the downstream cost savings that would be generated is all well and good, but funding for healthcare is stretched in almost all settings so may be challenging to operationalise in practice.

It is also important to consider the second limiting factor related to the excess demand for donor milk: a lack of donors. Recruitment of donors needs to be an on-going process, as there is inevitably a limit to the time period in which a woman can be a donor. Work to explore how the number of donors can be increased – while maintaining the necessary safeguards – would therefore be useful, bearing in mind that some interventions to increase supply, such as collection from a donor's home, will add to the cost of providing donor milk and therefore reduce its cost-effectiveness.

Conclusion

Our results have not provided one unique answer to the question of how to allocate donor human milk between VLBW, because the answer depends on whether the decision-maker prioritises saving lives or money. One option is to prioritise saving money in the short-term to use the savings to invest in the milk banking infrastucture for the long-term; but this solution still raises a number of ethical and practical considerations. In addition, our results cannot be considered definitive. We therefore hope that others will use our model to re-populate it with their own data and update it as new evidence becomes available.

KEY MESSAGES

The use of donor human breast milk is a cost-effective alternative to the use of formula milk when a mother's own milk is unavailable or limited in supply.

When the supply of donor milk is limited, lives saved can be maximised by prioritising infants with the lowest birthweights (<1,000g) and then using additional supplies to give slightly heavier babies donor milk for 14 days before giving it to the lightest babies for 28 days. Cost savings can be maximised by prioritising infants with birthweights >1000g**.**

Decision-makers may have to choose between saving the most lives and saving the most money.

Figure

Figure 1: Example decision tree (1,251-1,500g birthweight group)

Legend: Each block represents one week of time

REFERENCES

Arnold, L. D. (2002). The cost-effectiveness of using banked donor milk in the neonatal intensive care unit: prevention of necrotizing enterocolitis. Journal of Human Lactation, 18, 172-177.

Arslanoglu, S., Corpeleijn, W., Moro, G., Braegger, C., Campoy, C., Colomb, V., . . . Hojsak, I. (2013). Donor human milk for preterm infants: current evidence and research directions. Journal of Pediatric Gastroenterology and Nutrition, 57, 535-542.

Boehler, C. E. H., & Lord, J. (2016). Mind the Gap! A Multilevel Analysis of Factors Related to Variation in Published Cost-Effectiveness Estimates within and between Countries. Medical Decision Making, 36, 31-47.

Briggs, A., Claxton, K. & Sculpher, M. (2006). Decision modelling for health economic evaluation. Oxford: Oxford University Press.

British Association of Perinatal Medicine. (2015). The Use of Donor Human Expressed Breast Milk in Newborn Infants: A Framework for Practice. Retrieved January 12 2017, from http://www.bapm.org/publications/documents/guidelines/DEBM%20framework%20draft%20for%20consultation.pdf

Brown, J., Embleton, N., Harding, J., & McGuire, W. (2016). Multi-nutrient fortification of human milk for preterm infants. Cochrane Database of Systematic Reviews, 5, CD000343.

Buckle, A., & Taylor, C. (2017). Cost and cost-effectiveness of donor human breast milk for the prevention of necrotising enterocolitis: Systematic review. Breastfeeding Medicine, in press.

Department of Health. (2014). National Schedule of Reference Costs 2013-14. London: Department of Health.

Eidelman, A. I., Schanler, R. J., Johnston, M., Landers, S., Noble, L., Szucs, K., & Viehmann, L. (2012). Breastfeeding and the Use of Human Milk. Pediatrics, 129, e827-e841.

Fitzgibbons, S. C., Ching, Y., Yu, D., Carpenter, J., Kenny, M., Weldon, C., . . . Jaksic, T. (2009). Mortality of necrotizing enterocolitis expressed by birth weight categories. Journal of Pediatric Surgery, 44, 1072-1076.

Grant, R. L. (2014). Converting an odds ratio to a range of plausible relative risks for better communication of research findings. BMJ, 348, f7450.

Guthrie, S. O., Gordon, P. V., Thomas, V., Thorp, J. A., Peabody, J., & Clark, R. H. (2003). Necrotizing enterocolitis among neonates in the United States. Journal of Perinatology, 23, 278-285.

Hagadorn, J. I., Brownell, E. A., Lussier, M. M., Parker, M. G., & Herson, V. C. (2016). Variability of Criteria for Pasteurized Donor Human Milk Use A Survey of US Neonatal Intensive Care Unit Medical Directors. Journal of Parenteral and Enteral Nutrition, 40, 326-333.

Hull, M. A., Fisher, J. G., Gutierrez, I. M., Jones, B. A., Kang, K. H., Kenny, M., . . . Jaksic, T. (2014). Mortality and management of surgical necrotizing enterocolitis in very low birth weight neonates: a prospective cohort study. Journal of the American College of Surgeons, 218, 1148-1155.

Husereau, D., Drummond, M., Petrou, S., Carswell, C., Moher, D., Greenberg, D., . . . Loder, E. (2013). Consolidated health economic evaluation reporting standards (CHEERS) statement. Cost Effectiveness and Resource Allocation, 11(1), 6.

International Federation of Health Plans. (2015). 2015 Comparative Price Report: Variation in medical and hospital prices by country. London, International Federation of Health Plans.

Jegier, B. J., Meier, P., Engstrom, J. L., & McBride, T. (2010). The initial maternal cost of providing 100 mL of human milk for very low birth weight infants in the neonatal intensive care unit. Breastfeeding Medicine, 5, 71-77.

Lango, M. O., Horn, A. R., & Harrison, M. C. (2013). Growth velocity of extremely low birth weight preterms at a tertiary neonatal unit in South Africa. Journal of Tropical Pediatrics, 59, 79-83.

Lin, P. W., & Stoll, B. J. (2006). Necrotising enterocolitis. The Lancet, 368, 1271-1283.

Medo, E. T. (2013). Increasing the global supply and affordability of donor milk. Breastfeeding Medicine, 8, 438-441.

Meier, P., Patel, A., & Esquerra-Zwiers, A. (2017). Donor Human Milk Update: Evidence, Mechanisms, and Priorities for Research and Practice. The Journal of Pediatrics, 180, 15-21.
Miracle, D. J., Szucs, K. A., Torke, A. M., & Helft, P. R. (2011). Contemporary ethical issues in human milk-banking in the United States. Pediatrics, 128, 1186-1191.
Morgan, J., Young, L., & McGuire, W. (2015). Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database of Systematic Reviews, 10, CD001241.
NICE. (2010). CG93 Donor milk banks: service operation. London: National Institute for Health and Clinical Excellence.
Pattinson, R., & Rhoda, N., for the PPIP group. (2014). Saving Babies 2012-2013: Ninth report on perinatal care in South Africa. Pretoria: Tshepesa Press.
PSSRU. (2014). Unit costs of health and social care 2013-14. Canterbury: Personal Social Services Research Unit.
Quigley, M., & McGuire, W. (2014). Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrande Database of Systematic Reviews, CD002971.
Renfrew, M., Craig, D., Dyson, L., McCormick, F., Rice, S., King, S., . . . Williams, A. (2009). Breastfeeding promotion for infants in neonatal units: a systematic review and economic analysis. Health Technology Assessment, 13(40), 1-146.
Republic of South Africa. (2016). Government Gazette Vol. 610 No. 39955. Retrieved November 10 2016, from http://www.labour.gov.za/DOL/downloads/legislation/notices/medical-tariffs/2016/39955_%20Ambulance.pdf
Sabin, L. L., Knapp, A. B., MacLeod, W. B., Phiri-Mazala, G., Kasimba, J., Hamer, D. H., & Gill, C. J. (2012). Costs and Cost-Effectiveness of Training Traditional Birth Attendants to Reduce Neonatal Mortality in the Lufwanyama Neonatal Survival Study (LUNESP). PLoS ONE, 7, e35560.
Tan-Torres Edejer, T., Baltussen, R., Adam, T., Hutubessy, R., Acharya, A., Evans, D. B., Murray, C. J. L. (2003). Making choices in health: WHO guide to cost effectiveness analysis. Geneva: World Health Organization.
Tully, M. R. (2002). Recipient prioritization and use of human milk in the hospital setting. Journal of Human Lactation, 18, 393-396.
UNICEF. (1995). Baby Friendly Initiative. Retrieved November 9 2016, from www.unicef.org.uk/babyfriendly/what-is-baby-friendly/
WHO Commission on Macroeconomics and Health. (2001). Macroeconomics and health: investing in health for economic development. Report of the Commission on macroeconomics and health. Geneva: World Health Organization.
Wight, N. E. (2001). Donor human milk for preterm infants. Journal of Perinatology, 21, 249-254.
Williams, T., Nair, H., Simpson, J., & Embleton, N. (2016). Use of Donor Human Milk and Maternal Breastfeeding Rates A Systematic Review. Journal of Human Lactation, 32, 212-220.
World Bank. (2015a). GDP (PPP) (NY.GDP.PCAP.PP.CD). Retrieved October 4 2016, from http://databank.worldbank.org/
World Bank. (2015b). PPP conversion factor, GDP (LCU per international $) (PA.NUS.PPP). Retrieved November 6 2016, from http://databank.wordlbank.org/
Yee, W. H., Soraisham, A. S., Shah, V. S., Aziz, K., Yoon, W., & Lee, S. K. (2012). Incidence and timing of presentation of necrotizing enterocolitis in preterm infants. Pediatrics, 129, e298-e304.
Zipitis, C. S., Ward, J., & Bajaj, R. (2015). Use of donor breast milk in neonatal units in the UK. Archives of Disease in Childhood – Fetal and Neonatal Edition, 100, F279-F281.

Table 1: Parameter values in basecase and distributions used in the probabilistic sensitivity analysis

Variable	Birthweight group/cost type	Basecase value (95% credible interval from PSA)	Probabilistic sensitivity analysis (PSA) distribution and parameter values
Proportion of infants	500-750g	0.198 (0.191 to 0.205)	Dirichlet (2,153, 2,491, 2,888, 3,342)
	751-1,000g	0.229 (0.222 to 0.237)	
	1,001-1,250g	0.266 (0.257 to 0.274)	
	1,251-1,500g	0.307 (0.299 to 0.316)	
Mean birthweight (g)	500-750g	667	N/A
	751-1,000g	917	
	1,001-1,250g	1,167	
	1,251-1,500g	1,417	
Feeding duration for donor milk (days)	500-750g	0, 14, 28	N/A
	751-1,000g	0, 14, 28	
	1,001-1,250g	0, 14, 28	
	1,251-1,500g	0, 14	
Risk of NEC with formula milk	500-750g	0.120 (0.115 to 0.126)	Beta (1,568, 11,482)
	751-1,000g	0.092 (0.088 to 0.097)	Beta (1,569, 15,454)
	1,001-1,250g	0.057 (0.053 to 0.060)	Beta (1,063, 17,731)
	1,251-1,500g	0.033 (0.031 to 0.035)	Beta (758, 22,212)
Relative risk of any NEC with donor milk		0.360 (0.187 to 0.675)	Log normal (-1.019, 0.347)
Relative risk of surgical NEC with donor milk		0.700 (0.551 to 0.891)	Log normal (-0.351, 0.124)
NEC timing, severity and mortality		See Appendix table 1	N/A
Non-NEC mortality	500-750g	0.548	N/A
	751-1,000g	0.115	
	1,001-1,250g	0.005	
	1,251-1,500g	0.019	
Milk costs/ml (2015 USD at PPP)	Formula	0.0529	N/A
	Donor	0.1371	
Milk volumes by outcome and birthweight group		See Appendix table 4	N/A
Cost of care per day (2015 USD at PPP)	NICU	UK: 1,636; SA: 794	N/A
	High care	UK: 1,228; SA: 596	
	Normal care	UK: 681; SA: 330	
Other health care costs (2015 USD at PPP)	Surgery per operation	UK: 902; SA: 437	N/A
	Transfer per operation each way	1,162	
	Parenteral nutrition set-up	254	
	Parenteral nutrition per day	127	
Length of stay and NEC costs by outcome and birthweight group		See Appendix tables 5 & 6	N/A

Note: For sources and explanations of how distributions for the PSA were derived, please refer to the methods section; SA: South Africa.

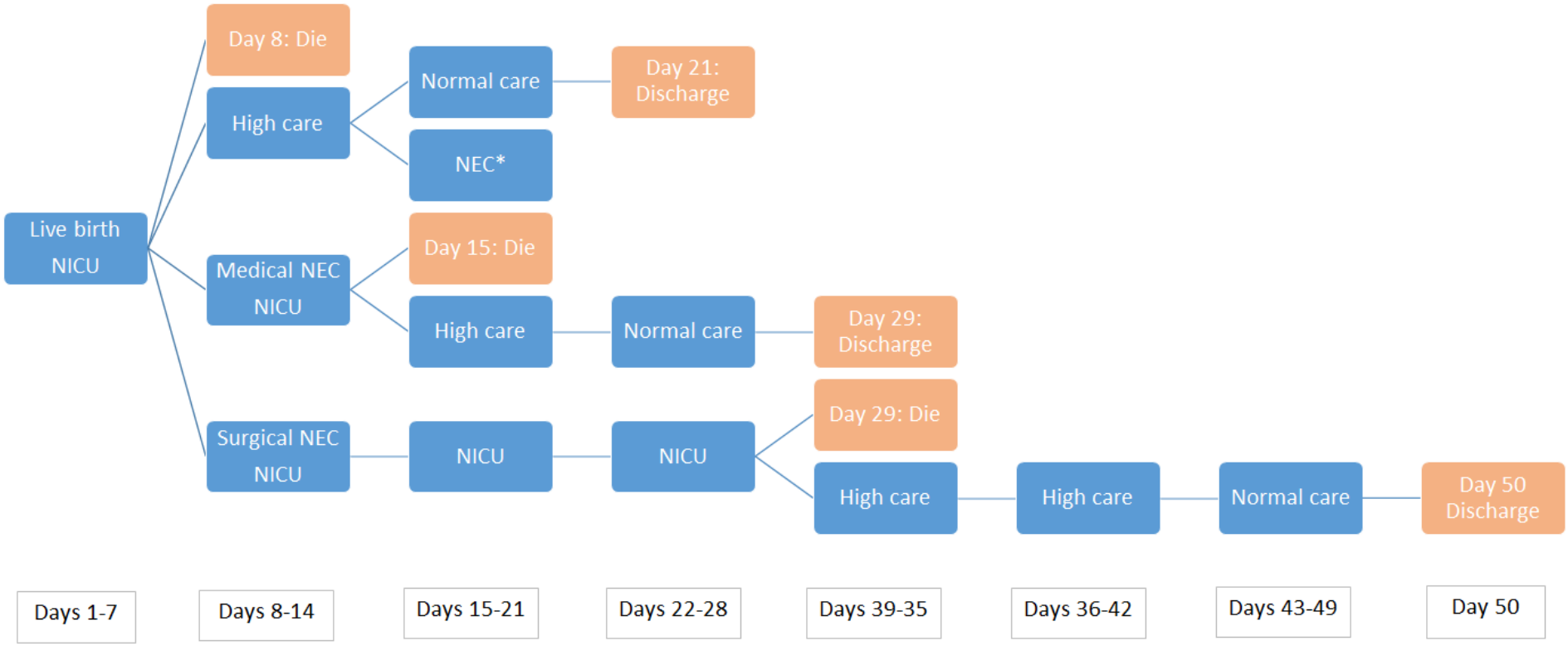
Table 2: Allocating donor milk to maximise the number of lives saved

Donor milk availability group (per 10,000 VLBW infants)	**Optimal allocation scenario**				**Mean lives saved (95% Credible Interval)**	**Probability that scenario is optimal**
BW Group (g):	500-750	710-1,000	1,001-1,250	1,251-1,500		
<5,000L	14	14	0	0	86 (45 to 113)	0.921
<10,000L	28	14	0	0	127 (66 to 168)	0.996
<15,000L	28	14	14	0	162 (85 to 214)	0.996
<20,000L	28	28	14	0	191 (100 to 252)	0.996
<25,000L	28	28	14	0	191 (100 to 252)	0.614
<30,000L	28	28	28	0	200 (105 to 264)	0.996
<35,000L	28	28	14	14	220 (115 to 290)	0.996
≥35,000L	28	28	28	14	229 (119 to 301)	0.996

Table 3: Allocating donor milk to minimise incremental costs

Donor milk availability group (per 10,000 VLBW infants)	**Optimal allocation scenario (days of donor milk to infants in each birthweight group, UK costs)**				**Mean incremental cost (2015 USD at PPP)**	**Probability that scenario is optimal**	**Optimal allocation scenario (days of donor milk to infants in each birthweight group, South African costs)**				**Mean incremental cost (2015 USD at PPP)**	**Probability that scenario is optimal**
BW Group (g):	500-750	710-1,000	1,001-1,250	1,251-1,500			500-750	710-1,000	1,001-1,250	1,251-1,500		
<5,000L	0	14	0	0	298,823	0.899	28	0	0	0	146,098	0.942
<10,000L	0	0	14	0	-824,987	0.985	0	0	14	0	-182,069	0.958
<15,000L	0	0	14	0	-824,987	0.980	0	0	14	0	-182,069	0.876
<20,000L	0	0	14	14	-1,249,641	0.924	0	0	14	0	-182,069	0.793
<25,000L	0	0	14	14	-1,249,641	0.923	0	0	14	0	-182,069	0.793
<30,000L	0	0	14	14	-1,249,641	0.883	0	0	14	0	-182,069	0.793
<35,000L	0	0	14	14	-1,249,641	0.883	0	0	14	0	-182,069	0.793
≥35,000L	0	0	14	14	-1,249,641	0.883	0	0	14	0	-182,069	0.793

Note: negative values represent cost savings.



* These NEC branches replicate those occuring at day 7 (i.e. include both types of NEC). The total length of stay for any neonate acquiring NEC is the same (by type of NEC) regardless of timing of onset, so the maximum length of stay for an infant in this birthweight group would be 56 days (discharge on day 57); for an infant acquiring surgical NEC on day 14.

Appendix table 1: Scenarios included in analysis (days on donor milk given to all infants in each birthweight group)

	Birthweight group					DM availability group (DM available per 10,000 VLBW infants)
Scenario	500-750g	751-1,000g	1,001-1,250g	1,251-1,500g	Total infants fed any DM/10,000	
	1,979	2,292	2,655	3,074		
Comparator	0	0	0	0	0	N/A
1	14	0	0	0	1,979	<5,000L
2	28	0	0	0	1,979	<5,000L
3	0	14	0	0	2,292	<5,000L
4	14	14	0	0	4,271	<5,000L
5	28	14	0	0	4,271	<10,000L
6	0	0	14	0	2,655	<10,000L
7	14	0	14	0	4,634	<10,000L
8	0	28	0	0	2,292	<10,000L
9	28	0	14	0	4,634	<10,000L
10	0	0	0	14	3,074	<15,000L
11	14	28	0	0	4,271	<15,000L
12	0	14	14	0	4,947	<15,000L
13	14	0	0	14	5,053	<15,000L
14	14	14	14	0	6,926	<15,000L
15	28	28	0	0	4,271	<15,000L
16	28	0	0	14	5,053	<15,000L
17	28	14	14	0	6,926	<15,000L
18	0	14	0	14	5,366	<15,000L
19	14	14	0	14	7,345	<20,000L
20	0	0	28	0	2,655	<20,000L
21	0	28	14	0	4,947	<20,000L
22	28	14	0	14	7,345	<20,000L
23	14	0	28	0	4,634	<20,000L
24	0	0	14	14	5,729	<20,000L
25	14	28	14	0	6,926	<20,000L
26	14	0	14	14	7,708	<20,000L
27	28	0	28	0	4,634	<20,000L
28	28	28	14	0	6,926	<20,000L
29	0	14	28	0	4,947	<25,000L
30	0	28	0	14	5,366	<25,000L
31	28	0	14	14	7,708	<25,000L
32	14	14	28	0	6,926	<25,000L
33	14	28	0	14	7,345	<25,000L
34	0	14	14	14	8,021	<25,000L
35	14	14	14	14	10,000	<25,000L
36	28	14	28	0	6,926	<25,000L
37	28	28	0	14	7,345	<25,000L
38	28	14	14	14	10,000	<25,000L
39	0	28	28	0	4,947	<30,000L
40	0	0	28	14	5,729	<30,000L
41	14	28	28	0	6,926	<30,000L
42	0	28	14	14	8,021	<30,000L
43	14	0	28	14	7,708	<30,000L
44	14	28	14	14	10,000	<30,000L
45	28	28	28	0	6,926	<30,000L
46	28	0	28	14	7,708	<35,000L
47	28	28	14	14	10,000	<35,000L
48	0	14	28	14	8,021	<35,000L
49	14	14	28	14	10,000	<35,000L
50	28	14	28	14	10,000	<35,000L
51	0	28	28	14	8,021	>=35,000L
52	14	28	28	14	10,000	>=35,000L
53	28	28	28	14	10,000	>=35,000L

Note: The scenarios are ordered in ascending total donor milk volume required.

Appendix table 2: Distributions of NEC timing, severity and mortality by birthweight group (proportion of NEC cases)

	500-750g	**751-1,000g**	**1,001-1,250g**	**1,251-1,500g**
Timing of onset				
Week 1	0.20	0.30	0.50	0.65
Week 2	0.30	0.30	0.30	0.35
Week 3	0.30	0.30	0.15	0
Week 4	0.20	0.10	0.05	0
Severity and mortality				
Palliative	0.25	0.25	0	0
Medical – survive	0.30	0.30	0.40	0.40
Medical – die	0.30	0.30	0.45	0.45
Surgical – survive	0.14	0.14	0.14	0.14
Surgical - die	0.01	0.01	0.01	0.01

Appendix table 3: Progression of feeding volumes by birthweight group

	500-750g	**751-1,000g**	**1,001-1,250g**	**1,251-1,500g**
Starting volume (ml/kg/day)	12	12	24	24
Increase per day (ml/kg/day)	12	24	36	48

Appendix table 4: Milk volumes for total hospital stay per infant (ml) by milk type, birthweight group and outcome

	Feeding volume, all formula milk				Feeding volume, up to 14 days donor milk								Feeding volume, up to 28 days donor milk					
					Volume of donor milk				Volume of formula milk				Volume of donor milk			Volume of formula milk		
	500-750g	751-1,000g	1,001-1,250g	1,251-1,500g	500-750g	751-1,000g	1,001-1,250g	1,251-1,500g	500-750g	751-1,000g	1,001-1,250g	1,251-1,500g	500-750g	751-1,000g	1,001-1,250g	500-750g	751-1,000g	1,001-1,250g
No NEC survive	9,062	8,709	6,738	5,871	840	1,882	2,815	3,605	8,222	6,828	3,923	2,266	3,032	4,964	6,738	6,030	3,745	0
No NEC die	224	539	1,050	1,462	224	539	1,050	1,462	0	0	0	0	224	539	1,050	0	0	0
Medical NEC:																		
7 days survive	14,787	14,546	12,494	12,013	224	539	1,050	1,462	14,563	14,007	11,443	10,550	224	539	1,050	14,563	14,007	11,443
7 days die	224	539	1,050	1,462	224	539	1,050	1,462	0	0	0	0	224	539	1,050	0	0	0
14 days survive	14,386	14,422	12,392	11,889	840	1,882	2,815	3,605	13,546	12,540	9,577	8,284	840	1,882	2,815	13,546	12,540	9,577
14 days die	840	1,882	2,815	3,605	840	1,882	2,815	3,605	0	0	0	0	840	1,882	2,815	0	0	0
21 days survive	14,228	14,272	12,201	N/A	840	1,882	2,815	N/A	13,388	12,390	9,386	N/A	1,857	3,348	4,681	12,371	10,924	7,520
21 days die	1,857	3,348	4,681	N/A	840	1,882	2,815	N/A	1,017	1,466	1,866	N/A	1,857	3,348	4,681	0	0	0
28 days survive	14,108	14,107	11,991	N/A	840	1,882	2,815	N/A	13,268	12,225	9,176	N/A	3,032	4,964	6,738	11,076	9,142	5,253
28 days die	3,032	4,964	6,738	N/A	840	1,882	2,815	N/A	2,192	3,083	3,923	N/A	3,032	4,964	6,738	0	0	0
Surgical NEC:																		
7 days survive	21,085	21,076	18,640	18,343	224	539	1,050	1,462	20,861	20,537	17,590	16,880	224	539	1,050	20,861	20,537	17,590
7 days die	224	539	1,050	1,462	224	539	1,050	1,462	0	0	0	0	224	539	1,050	0	0	0
14 days survive	20,406	20,637	18,138	17,732	840	1,882	2,815	3,605	19,566	18,755	15,323	14,127	840	1,882	2,815	19,566	18,755	15,323
14 days die	840	1,882	2,815	3,605	840	1,882	2,815	3,605	0	0	0	0	840	1,882	2,815	0	0	0
21 days survive	19,996	20,140	17,505	N/A	840	1,882	2,815	N/A	19,156	18,258	14,690	N/A	1,857	3,348	4,681	18,139	16,792	12,824
21 days die	1,857	3,348	4,681	N/A	840	1,882	2,815	N/A	1,017	1,466	1,866	N/A	1,857	3,348	4,681	0	0	0
28 days survive	19,597	19,592	16,808	N/A	840	1,882	2,815	N/A	18,757	17,710	13,993	N/A	3,032	4,964	6,738	16,565	14,628	10,070
28 days die	3,032	4,964	6,738	N/A	840	1,882	2,815	N/A	2,192	3,083	3,923	N/A	3,032	4,964	6,738	0	0	0
Palliative NEC:																		
7 days	224	539	N/A	N/A	224	539	N/A	N/A	0	0	N/A	N/A	224	539	N/A	0	0	N/A
14 days	840	1,882	N/A	N/A	840	1,882	N/A	N/A	0	0	N/A	N/A	840	1,882	N/A	0	0	N/A
21 days	1,857	3,348	N/A	N/A	840	1,882	N/A	N/A	1,017	1,466	N/A	N/A	1,857	3,348	N/A	0	0	N/A
28 days	3,032	4,964	N/A	N/A	840	1,882	N/A	N/A	2,192	3,083	N/A	N/A	3,032	4,964	N/A	0	0	N/A

N/A: Based on the data in Appendix Table 2, these outcomes do not occur in the model: no infants >1,000g birthweight acquire palliative NEC and no infants >1,250g birthweight acquire NEC after the first two weeks of life.

Appendix table 5: Length of stay (LOS) in days by type of care by outcome and birthweight group

	500-750g	751-1,000g	1,001-1,250g	1,251-1,500g
No NEC – survive (total LOS)				
NICU	21	21	7	7
High care	21	14	7	7
Normal care	14	7	14	7
No NEC – die (total LOS)				
NICU	7	7	7	7
Palliative NEC (LOS following NEC diagnosis)				
NICU	2	2	N/A	N/A
Medical NEC - survive (additional LOS)				
NICU	7	7	7	7
High care	7	7	7	7
Normal care	7	7	7	7
Medical NEC – die (LOS following NEC diagnosis)				
NICU	7	7	7	7
Surgical NEC – survive (additional LOS)				
NICU	21	21	21	21
High care	14	14	14	14
Normal care	7	7	7	7
Surgical NEC – die (LOS following NEC diagnosis)				
NICU	21	21	21	21

NICU: Neonatal intensive care unit

Appendix table 6: Length of stay (days) by level of care, birthweight group and outcome and mean incremental cost of NEC

	NICU days				High care days				Normal care days				Mean incremental cost of NEC per infant, 2015 USD at PPP (including TPN but excluding milk costs) Comparator: No NEC survive			
	500-750g	751-1,000g	1,001-1,250g	1,251-1,500g	500-750g	751-1,000g	1,001-1,250g	1,251-1,500g	500-750g	751-1,000g	1,001-1,250g	1,251-1,500g	500-750g	751-1,000g	1,001-1,250g	1,251-1,500g
No NEC survive	21	21	7	7	21	14	7	7	14	7	14	7	N/A	N/A	N/A	N/A
No NEC die	7	7	7	7	0	0	0	0	0	0	0	0	N/A	N/A	N/A	N/A
Medical NEC:																
All survivors:														25,958		
7 days survive	28	28	14	14	28	21	14	14	21	14	21	14				
7 days die	14	14	14	14	0	0	0	0	0	0	0	0	- 45,633	- 32,272	- 5,529	- 765
14 days survive	28	28	14	14	28	21	14	14	21	14	21	14				
14 days die	21	21	14	14	0	0	7	7	0	0	0	0	- 34,178	- 20,817	3,068	7,832
21 days survive	28	28	14	N/A	28	21	14	N/A	21	14	21	N/A				
21 days die	28	28	14	N/A	0	0	7	N/A	0	0	7	N/A	- 22,723	- 9,361	7,832	12,597
28 days survive	28	28	14	N/A	28	21	14	N/A	21	14	21	N/A				
28 days die	28	28	14	N/A	7	7	7	N/A	0	0	14	N/A	- 14,126	- 765	12,597	1,141
Surgical NEC:																
All survivors:														67,524		
7 days survive	42	42	28	28	35	28	21	21	21	14	21	14				
7 days die	28	28	28	28	0	0	0	0	0	0	0	0	- 18,186	- 4,825	21,918	26,683
14 days survive	42	42	28	28	35	28	21	21	21	14	21	14				
14 days die	35	35	28	28	0	0	7	7	0	0	0	0	- 6,731	6,631	30,515	35,280
21 days survive	42	42	28	N/A	35	28	21	N/A	21	14	21	N/A				
21 days die	42	42	28	N/A	0	0	7	N/A	0	0	7	N/A	4,725	18,086	35,280	40,044
28 days survive	42	42	28	N/A	35	28	21	N/A	21	14	21	N/A				
28 days die	42	42	28	N/A	7	7	7	N/A	0	0	14	N/A	13,322	26,683	40,044	5,678
Palliative NEC:																
7 days	9	9	N/A	N/A	0	0	N/A	N/A	0	0	N/A	N/A	- 54,450	- 41,089	N/A	N/A
14 days	16	16	N/A	N/A	0	0	N/A	N/A	0	0	N/A	N/A	- 42,994	- 29,633	N/A	N/A
21 days	23	23	N/A	N/A	0	0	N/A	N/A	0	0	N/A	N/A	- 31,539	- 18,178	N/A	N/A
28 days	23	23	N/A	N/A	7	7	N/A	N/A	0	0	N/A	N/A	- 22,942	- 9,581	N/A	N/A

N/A: Based on the data in Appendix Table 2, these outcomes do not occur in the model: no infants >1,000g birthweight acquire palliative NEC and no infants >1,250g birthweight acquire NEC after the first two weeks of life.
TPN: Total parenteral nutrition.