Cost and cost-effectiveness of donor human milk to prevent necrotizing enterocolitis: Systematic review

Running title: Cost and cost-effectiveness of donor human milk

Abigail Buckle, BSc and Celia Taylor, PhD*

Division of Health Sciences, University of Warwick, Coventry, CV4 7AL, UK

* Corresponding author: email: celia.taylor@warwick.ac.uk; tel: 00442476524793

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Abstract

Background: Necrotizing enterocolitis (NEC) is a costly gastrointestinal disorder that mainly affects preterm and low birth weight infants and can lead to considerable morbidity and mortality. Mother's own milk is protective against NEC but is not always available. In such cases, donor human milk has also been shown to be protective (albeit to a lesser extent) compared with formula milk, but is more expensive. This systematic review aimed to evaluate the cost of donor milk, the cost of treating NEC and the cost-effectiveness of exclusive donor milk vs formula milk feeding to reduce the short-term health and treatment costs of NEC.

Methods: We systematically searched five relevant databases to find studies with verifiable costs or charges of donor milk and/or treatment of NEC and any economic evaluations comparing exclusive donor milk with exclusive formula milk feeding. All search results were double-screened.

Results: Six studies with verifiable donor milk costs and 17 with verifiable NEC treatment costs were included. The types of cost or charge included varied considerably across studies so quantitative synthesis was not attempted. Estimates of the excess length of stay associated with NEC were approximately 18 days for medical NEC and 50 days for surgical NEC. Two studies claimed to report economic evaluations but did not do so in practice.

Conclusions: It is likely that donor milk provides short-term cost savings by reducing the incidence of NEC. Future studies should provide more details on cost components

included and a full economic evaluation including long-term outcomes should be undertaken.

Introduction

Globally, approximately 1.1m preterm (<37 weeks gestation) infants die each year, with the infant mortality rate for preterm infants at least three times that for term infants[1]. One condition mainly affecting preterm or low birth weight (<2,500g) infants is necrotizing enterocolitis (NEC)[2]. The incidence of NEC in developed countries is up to 13% amongst low birth weight infants and/or those born before 33 weeks[2]. NEC is usually treated medically with bowel rest and systemic antibiotics but more severe cases are treated surgically via peritoneal drainage and laparotomy[2,3]. A systematic review suggested an overall mortality rate of around 20%[4], with up to five-fold higher mortality amongst those requiring surgery[5].

Many agree that breast milk is a natural prophylactic for NEC[6-8] and mother's own breast milk is clearly the optimal choice for all infants for this, plus many other reasons[9]. However, mothers with preterm babies may not be able to produce enough milk, may be too ill to breastfeed or may die in childbirth[10]. In this situation, the World Health Organization and others recommend using donor human breast milk (donor milk) which confers a number of advantages over the alternative of formula milk[9,11-13]. A recent systematic review[7] reports that donor milk reduces the risk of NEC by almost two-thirds compared with formula. However, not all preterm babies who do not receive their mother's own milk receive donor milk instead[14,15]. Donor milk is more expensive than formula and while it confers various health benefits, it is not known whether its use is cost-effective[16-18].

We therefore undertook a systematic review to answer the following questions:

1. What is the cost of donor milk?

2. What is the initial cost to the health service of treating medical and surgical NEC?

3. Is exclusive donor milk feeding cost-saving and/or cost-effective compared to exclusive formula milk feeding when considering its impact on the short-term cost and health outcomes associated with NEC?

Materials and Methods

The protocol was registered on PROSPERO (reference number CRD42016042581).

Eligibility criteria

- Participants: All infants
- Intervention: Exclusive donor human breast milk
- Comparison (for economic evaluation studies): Exclusive formula milk
- Outcomes: Cost of donor milk, short-term health service cost of treating NEC (medical and surgical), cost-effectiveness of donor milk in terms of the short-term health and health service costs of NEC. We did not specify a definition of NEC. Short-term is defined as the time from birth to initial post-natal discharge. Costs data had to be 'verifiable' i.e. specified the data source. We sought costs data but included charges (to the patient or other payer) if costs were not reported.

- Study design: Any study reporting costs of donor milk and/or NEC, or any form of economic evaluation. Protocols, opinion pieces/editorials and abstracts were excluded.
- Language and date: Due to resource constraints, only English language studies were included. We only sought studies published since January 1996 to recognise expected changes in cost structures over time.
- Publication status: Grey literature was sought.

Search methods

We carried out two search strategies; the first to identify costs of donor milk and the second to identify costs of treating NEC. Both search strategies were also used to identify studies including any form of economic evaluation. For both searches the following databases were used: CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Medline and Google Scholar. The last searches were undertaken on 11/10/16 for donor milk and 25/10/16 for NEC costs. AB conducted the searches.

Our broad search terms (as title or keyword) were as follows:

- Donor milk: We used a combination of [Human milk or donor milk or donor human milk or donor breast milk or milk bank*] AND [cost or economic* or value or budget or fee or saving or income or price or expense].
- NEC: We used a combination of [NEC or necrotising enterocolitis or necrotizing enterocolitis] AND [cost or economic* or value or budget or fee or saving or income or price or expense].

The full search strategy can be found in Supplementary File 1. For both searches, the references of any relevant reviews or studies meeting the eligibility criteria were checked to identify any further studies/sources.

Study selection

The search results were de-duplicated using EndNote v7. Both authors independently screened all of the titles and abstracts against the eligibility criteria. All studies that either author thought should be included were added to a full text list. These studies were then read independently in full and each author made a decision on whether or not each study should be included. Discrepancies were discussed until agreement was reached.

Data collection process and data items

Data extraction was initially undertaken by AB and checked by CT. A data extraction template was designed in Excel for each of the donor milk and NEC treatment costs research questions including the following details:

- Donor milk: cost, units, year of costing, country/currency, cost components included (e.g. transport, payments to donors) and whether cost or charge.
- NEC treatment: cost by type (medical/surgical), year of costing, country/currency, cost components included (e.g. indirect costs such as "hotel" or overhead costs and physician fees), whether data were collected from a primary research study (i.e. with individual infants) or from a secondary source (i.e. generalised costings), sample size for primary studies, infants included/excluded (e.g. by birth weight, early mortality),

definition of NEC, cost sources, whether cost or charge, whether costs/charges were adjusted for infant characteristics (in primary studies) and whether total cost of treatment or incremental (compared with an infant without NEC). We also extracted data on the length of stay associated with NEC.

Costs as opposed to charges, and incremental rather than total values were extracted if both were provided; although total (non-incremental) values were also extracted where these provided more detailed results (e.g. a breakdown by type of NEC or standard deviations). Values adjusted for infant characteristics were reported where available. For NEC treatment costs, the mean and standard deviation costs/charges were reported where provided. Exceptions (e.g. where a study only reported median values) were noted. For the economic evaluation studies, we planned to summarise information on sources of costs and effectiveness data and the methods used in calculating cost savings or cost-effectiveness, together with study results and details of any sensitivity analysis.

Strategy for data synthesis

All costs were inflated to 2015 local currency units and converted to 2015 US Dollars at purchasing power parity (PPP) using the World Bank Consumer Price Index and exchange rates[1919]. For each estimate of the cost of donor milk, we calculated the cost per 100ml as well as an indicative cost per infant in two scenarios. The first scenario was use with an infant with birth weight 500-1,250g fed only with donor milk for their initial hospital stay, based on a total consumption of 11 litres as estimated from the data presented in Cristofalo et al.'s recent randomised controlled trial[20]. The second scenario was use of donor milk for an average infant <33 weeks or <1500g admitted to neonatal intensive care, using the mean consumption of 2.1 litres per infant from Carroll and Herrman's study[21]. The volume of donor milk per infant varied considerably in this study (range 3-9,271ml where used; 28% received none) and was dependent on the method of feeding at discharge. However, we use the overall mean (including infants who did not receive any donor milk) because it is not always possible to know an infant's method of feeding at discharge at the time donor milk would be initiated (and the ethics of rationing use to only those mothers definitely intending or able to breastfeed are also questionable). We aimed to synthesise data on donor milk and NEC treatment costs by calculating mean costs across studies where there were sufficient comparable studies available, using appropriate sub-groups (e.g. by country) if necessary. Where comparable data were not available, quantitative synthesis did not occur and a descriptive analysis was carried out. The results of the economic evaluation studies were summarised individually.

Results

Study selection

The numbers of studies screened, assessed for eligibility and included and excluded in the review can be seen in Figure 1.

Cost of donor milk

Seven estimates of the cost of donor milk were reported across six studies[4,21-26]. The cost per 100ml donor milk in each study can be seen in Table 1**.** Only one study reported the cost of production[4], which at $51/100ml was actually considerably larger than any of the studies reporting charges (to the health service). The authors noted that improvements in how the milk banking service was organised could reduce this cost to a more comparable $21/100ml[4]. As most milk banks are not for profit we would expect there to be little practical difference between costs and charges, with the latter ranging from $8/100ml[26] to $21/100ml[25]. The lowest two charges were actually those from milk banking services that made a monetary payment to donors to compensate them for the time and effort required to pump milk[26]. Although the small number of studies from any one country or region warrants caution, donor milk appears to be particularly expensive in the UK compared to in the US and Scandinavia. We calculated the mean cost for the four US studies ($14 per 100ml, with indicative costs of $1,500 per infant fed only on donor milk and $286 per infant), but note that the four estimates differed in terms of the cost components included. Due to large variation in costs between settings we did not attempt any further quantitative synthesis.

<u>NEC Treatment costs and length of stay</u>

A total of 17 studies reported one or more values for NEC treatment costs[3,4,6,23,25,27-38]. Table 2 details the NEC treatment costs and length of stay in each study separated by whether costs/charges were provided and whether these were incremental to those for an infant without NEC or total costs for an infant with NEC. Further characteristics of each study, including the definition of NEC employed (if provided), can be found in

Supplementary File 2. Due to the variation between studies in infant birth weight, definition of NEC, type of NEC treatment including the specific surgical procedure, which cost components were included, and healthcare context, there is a very large overall range of results in Table 2 and quantitative synthesis of costs data was not thought to be appropriate. For example, the lowest value of $3,025 was for the incremental cost of medical NEC (no definition provided) excluding indirect, “hotel” and physician costs[32], while the highest value of $604,526 was for the total charge for small bowel surgery (using ICD-9 code 777.5)[37]. Even between two seemingly comparable US studies, reported one year apart, the incremental cost of medical NEC had a five-fold variation, from $14,511[29] to $77,948[23]. NEC treatment costs also appear variable within studies. Where means and standard deviations were reported, the coefficient of variation ranged from 0.20 (incremental costs for surgical NEC from Ganapathy et al.[23]) to 0.98 (total charges for large bowel surgery from Zhang et al.[37]) although values of 0.3 to 0.4 were typical.

Length of stay data are more comparable between studies. Three studies reported estimated median total (non-incremental) length of stay for surgical NEC based on primary data collection[3,31,36], which ranged from 51 to 104 days. One further study reported an estimate of the mean of this parameter of 72 days[37]. Based on the results of Bisquera et al.[38] and Ganapathy et al.[23], the incremental length of stay due to surgical NEC (compared to that for an infant without NEC) is likely to be around 50 days. Fewer studies reported primary data for medical NEC, with one estimate of total median length of stay of 36 days[36], of which around half are likely to be the incremental length of stay associated with NEC[23,38].

Economic evaluation of donor milk compared with formula milk

We initially identified three economic evaluations[4,32,39]. While none of these met all of our inclusion criteria, it is important to consider why and to discuss other limitations of the two studies that claimed to provide economic evaluations of the use of donor milk. Wight[32] presented a return on investment analysis for the use of donor milk for very low birth weight infants (<1,500g). Three outcomes were considered: NEC, sepsis and overall length of stay (for any reason related to the use of human milk rather than formula). The analysis was based on local treatment costs of NEC and sepsis and daily "hotel" costs, but excluding physician fees. The unit cost of donor milk was provided by the local milk bank. Effectiveness data were taken from a single, non-randomised study comparing the use of fortified mother's own milk (not donor milk) with formula[40], which is problematic as donor milk is unlikely to be as effective as mother's own milk[4] (although for ethical reasons there are no "head-to-head" trials of donor milk vs. mother's own milk). In the economic analysis, infants could be fed with donor milk for either one or two months, although no rationale for these durations was provided and effectiveness was assumed to be equal regardless of duration of use. The method of calculating total milk requirements (2,000ml for one month or 7,100ml for two months) was not described. Formula milk was assumed to be free of charge. The year of costing was not specified and no sensitivity analysis was performed.

Arnold[39] claimed to present three models of the cost-effectiveness of banked donor milk for the prevention of NEC in preterm infants. The first model repeated Wight's results. The second model multiplied length of stay data from Schlaner et al.'s study[40] by 1997 daily Neonatal intensive care unit charges to give a length of stay-based charges saving. Donor milk unit costs were stated but could not be verified. Donor milk was assumed to be provided for 60 days (a rationale for this duration was not provided), although a clear description of how the total volume of donor milk required was included. Formula milk was assumed to be free of charge. No sensitivity analysis was performed. The third model claimed to calculate the preventable costs of NEC to the US state of Texas (i.e. comparing the cost of NEC in the scenario where all preterm infants were fed human milk (either mother's own milk or donor milk) to the current scenario where some infants were not fed with human milk but with formula instead). NEC costs were taken from Bisquera et al.'s study[38], although this study actually provides charges and not costs. No consideration of the cost of donor or formula milk was included, so this model cannot be described as an economic evaluation. The reduction in the incidence of NEC from the use of donor milk was calculated by subtracting the 1.2% risk of NEC in infants fed donor milk in a small randomised UK study[41] from the 10.1% risk of NEC for all infants (regardless of type of milk) in the US[42]. This is problematic because differences in study contexts reduce comparability and a failure to consider that the 10.1% risk for all infants is a weighted average of the risks for human and non-human milk and not a sum of the risks in these two feeding conditions.

The main intervention being evaluated in Renfrew et al.'s economic evaluation[4] was the provision of a lactation consultant to help mothers breastfeed their own infants. The use of donor milk was considered in a secondary analysis, as an adjunct to mother's own milk, so the comparison was not between exclusive use of donor milk and exclusive use of formula.

Discussion

We found six studies including verifiable costs or charges of donor milk. Four of these were conducted in the US and the mean cost of donor milk across these studies was approximately $14 per 100ml. Based on existing estimates of donor milk use[20,21], this would equate to costs of just under $300 per very low birth weight infant and of around $1,500 for an infant fed entirely on donor milk. We found 17 studies including initial costs to the health service/charges for the treatment of NEC; however there was insufficient comparability between the estimates provided to enable quantitative synthesis. Many studies did not even report what cost components were or were not included in their estimates. In particular, studies reporting the cost of donor milk did not include the fixed costs of setting up a milk bank (meaning the costs reported here are underestimates) or which specific tests on donors and their milk were undertaken. In addition, studies only reporting charges are particularly difficult to synthesise as cost to charge ratios vary between hospitals. Even within primary studies evaluating the cost of treating NEC, there was considerable variation between costs for individual infants suggesting that costs are also affected by a range of other factors/comorbidities. Future costing studies should clearly specify which costs are included, if possible using a "bottom-up" approach to costing.

Estimates of (excess) length of stay are easier to compare than NEC treatment costs and enable local bed-day costs to be applied by others wanting to estimate the financial impact of NEC on their own institution. The results of primary studies suggested that medical NEC would add around 18 days to an infant's length of stay and surgical NEC around 50 days.

It is, however, clear that the incremental costs of treating infants with NEC are large so any potential preventative measures are worthy of consideration. We were unable to include any economic evaluations of exclusive donor milk vs. formula milk in our review, even if we extended the outcomes included beyond NEC. Wight[32] and Arnold[39] both suggested that exclusive donor milk could be cost-saving and would therefore dominate the use of formula milk for preterm infants. However neither study is of sufficient methodological quality to provide convincing evidence of the cost-effectiveness of donor milk. Our protocol did not include the use of the results from our review of costs in a "back of the envelope" economic evaluation which could be subject to similar concerns regarding methodological quality. Therefore, while we believe it is likely that the use of donor milk would be at least cost-effective, and possibly also cost-saving compared with formula milk, we agree with others[16-18] that a full economic evaluation is warranted. Such an evaluation could consider both the use of exclusive donor milk vs. exclusive formula milk, different durations of donor milk feeding (with differential effectiveness) and/or the use of donor milk as a complement or 'top-up' to mother's own milk while breastfeeding is being established. It should include all the major short and long-term health (and associated cost) consequences related to the use of donor rather than formula milk (not just NEC) and potentially issues related to the acceptability of donor milk to parents[18,43,44]. While our results provide a starting point, any economic evaluation will need to clearly justify the costs of donor milk and NEC used as parameter inputs and, given the wide range of costs in the studies included in this review, it should include a range of sensitivity analyses to determine the robustness of the results to different costs of donor milk and NEC treatment. It may also be helpful to contact milk banks directly for costs data as part of an economic evaluation.

Our review is not without its limitations. On the cost of donor milk, we did not compare donor milk practices and organisation, health systems or breastfeeding cultures in each of the countries in which the included studies were undertaken and it may be that the large variation in costs is partially explained by such differences, which may even exist within countries. In the UK, for example, England tends to be served by local milk banks (N=14 nationwide) while one bank covers the whole of Scotland[45]. On the cost of NEC, we did not specifically search for studies assessing length of stay that did not also include costs so we may have missed some primary studies. On economic evaluations, our inclusion criteria meant that only studies comparing the use of exclusive donor vs. formula milk were included. The use of exclusive donor milk is rare in practice (but may occur, for example, where a mother dies in childbirth or is HIV positive and cannot safely breastfeed). This restriction was intended to ensure a consistent comparator so that we could synthesis results across studies but may mean we have excluded studies that would have provided an insight into the cost-effectiveness of donor milk. We did not compare donor milk with mother's own milk because the latter would clearly dominate in an economic evaluation, being both cheaper and at least as effective. Using the idea of extended dominance, if exclusive donor milk was found to be cost-effective compared with formula, then using donor milk as an adjunct to mother's own milk would be even more so. This is because the cost of donor milk would be reduced by over 70% and health outcomes would be at least as good.

We focused on the incidence and short-term costs of NEC as the only outcome associated with the use of donor milk. It may also be the case that donor milk reduces the severity of NEC, although to claim this we currently need to generalise from the results of a study using mother's own milk[46]. There are many other potential benefits of human milk such as reduced neurodevelopmental complications, neonatal infections and improved cardiovascular health[47-50], as well as potential risks if safety standards are not maintained[17] and a possible link with slower weight gain[7]. These additional outcomes would have implications for both the costs and health outcomes associated with the use of donor milk. Spill-over effects should also be considered. One concern is that the provision of donor milk 'crowds out' mother's own milk and this reduces breastfeeding rates. However a recent systematic review suggests that this is not the case in practice[51]. The studies identified were all carried out in developed countries, which may limit the international generalisability of the findings and publication bias may also be a problem, particularly for any economic evaluations that did not find positive evidence of the use of donor milk. While we used Google Scholar in an attempt to find grey literature we were unable to evaluate the extent of publication bias. We may also have missed studies published in languages other than English. In an attempt to maximise the credibility of our findings, we excluded studies where costs could not be 'verified' i.e. traced back to their original source. However no other quality appraisal of costing studies was undertaken. We also excluded a study where donor milk was purchased on the open market rather than from an official milk bank[52].

Conclusion

It is likely that the use of donor milk is cost-effective. To strengthen the evidence base there is a need for a comprehensive economic evaluation of the use of donor milk, focusing on providing evidence in contexts where the use of donor milk is not currently standard practice. Such work should carefully describe how the costs of donor milk and of its implications for healthcare have been generated, given the variability in the estimates we have identified between contexts, and, for some outcomes, also within contexts.

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Corresponding author details

Celia Taylor, Division of Health Sciences, University of Warwick, Coventry, CV4 7AL, UK, email: celia.taylor@warwick.ac.uk; tel: 00442476524793.

Table 1. Cost/charge of donor milk per 100ml and indicative cost per infant (for exclusive use of donor milk and use as an adjunct to mother's own milk) and inclusions in cost/charge. All values are reported as 2015 USD at PPP. Cost/charge components marked as Y for included (value where provided), N for not included, and blank if not reported.

Author	Country	Cost/ 100ml	Cost per infant, exclusive donor milk (11l)	Cost per infant, donor milk as adjunct (2.1l)	Payment to donor?	Processing	Transport to User	Handling	Cost/Charge (to user)
Jegier et al.[22]	USA	14.41	1,585	303	N				Charge
Ganapathy et al.[23]	USA	10.68	1,175	224	N	Y	Y	Y	Charge
Carroll et al.[21]	USA	14.24	1,566	299	N		N		Charge
Huertas[24]	USA	15.21	1,673	319	N	Y			Charge
USA Mean	**USA**	**13.64**	**1,500**	**286**					
Renfrew et al.[4]	UK	51.05	5,612	1,072	N				Cost
Pokhrel et al.[25]	UK	21.30	2,343	447	N		4.81		Charge
Arnold[26]	Denmark	9.87	1,086	207	2.68				Charge
Arnold [26]	Sweden	8.04	884	169	1.67				Charge (out of county hospitals)

Note: Studies are ordered by country and then by date.

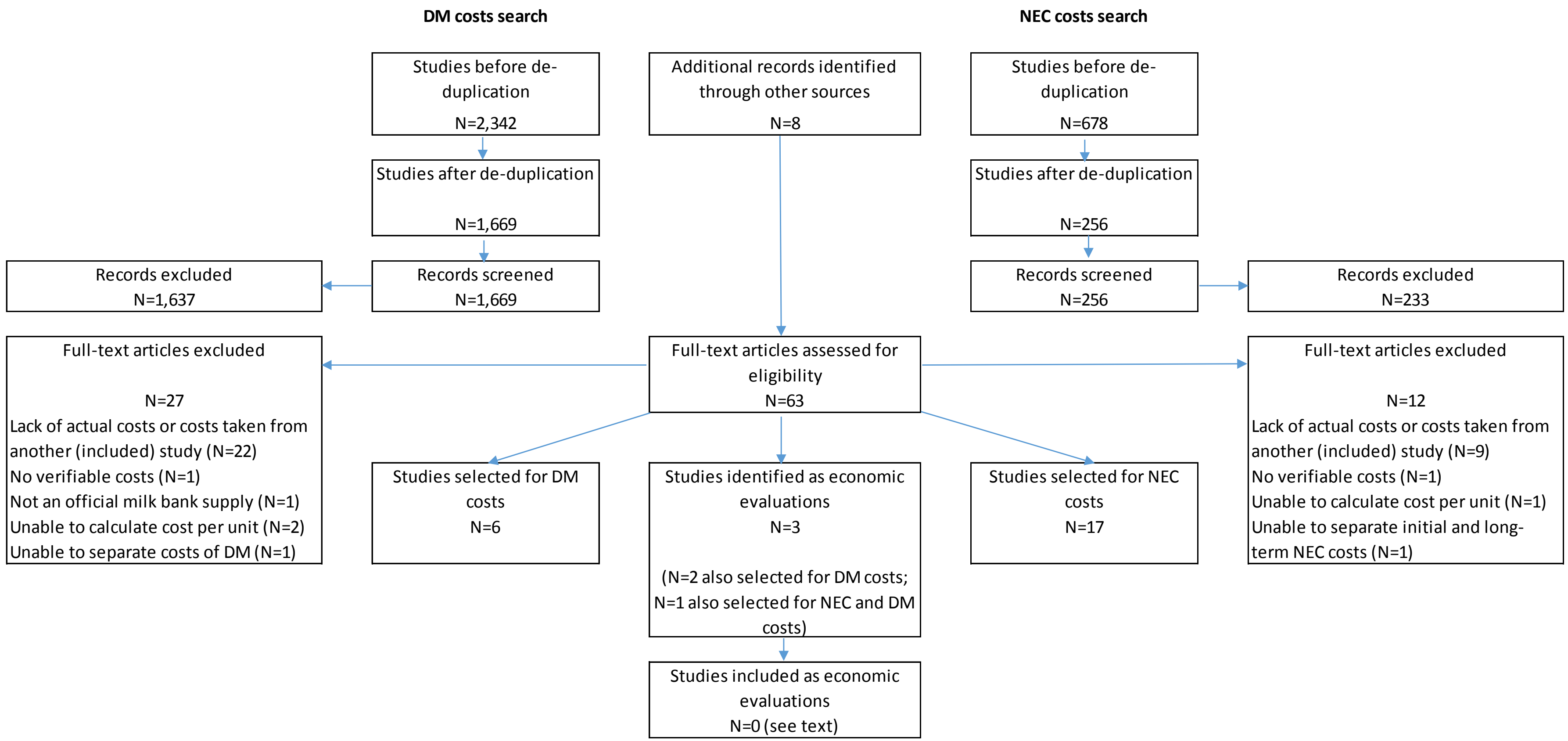
Table 2. Initial hospitalization costs/charges of NEC and inclusions in cost/charge (in addition to direct treatment costs). All costs/charges are reported as 2015 USD at purchasing power parity (PPP) and means are reported unless specified. Cost/charge components marked as Y for included, N for not included, and blank if not reported. Costs/charges are reported as means (±standard deviation)/reference values from secondary sources unless stated.

Author	Country	Birthweight	Total cost/ charge	Medical cost/charge	Surgical cost/charge	Indirect costs ("hotel"/overheads) included?	LOS	Physician fees included?	Primary (P) /Secondary (S) data
Total (non-incremental) costs/LOS									
Weimer[27]	USA	All			178,758	Y	39 days	N	S
Bartick et al.[28]	USA	1500-2499g		92,834		Y			S
Johnson et al.[29]	USA	<1500g	111,298 ± 46,217			Excl overheads	Mean 87 days	N	P
Johnson et al.[6]	USA	<1500g, <35 weeks gestation	185,980 ± 104,079	157,252 ± 64,614	323,875 ± 151,991	Y	Mean 85 days		P
Stey et al.[3] Peritoneal drainage	USA	All			280,987 ± 97,787	Y	Median 51 days		P
Stey et al.[3] Peritoneal drainage and laparotomy	USA	All			405,257 ± 133,903	Y	Median 104 days		P
Stey et al.[3] Laparotomy	USA	All			347,994 ± 108,844	Y	Median 91 days		P
Smith et al.[30]	Australia	1500-1999g	30,733			Y			S
Struijs et al. [31] Early closure	Netherlands	All			134,980 (Median)	Y	Median 100 days	Y	P
Struijs et al. [31] Late closure	Netherlands	All			140,209 (Median)	Y	Median 96 days	Y	P
Incremental costs/LOS									
Wight[32]	USA	All		3,025		N		N	S
Ganapathy et al.[23]	USA	≤ 28 weeks		77,948 ± 28,389	208,594 ± 40,846		Medical mean 12 days; Surgical mean 43 days	N	P
Johnson et al. [29]	USA	<1500g	17,056	14,511	24,665	Excl overheads	Difference in means 16 days	N	P
Johnson et al. [29]	USA	<750g	20,942			Y excluding overheads		N	P
Johnson et al. [29]	USA	750-999g	16,707			Y excluding overheads		N	P

Johnson et al.[29]	USA	1000-1249g	11,890			Y excluding overheads		N	P
Johnson et al. [29]	USA	1250-1499g	9,627			Y excluding overheads		N	P
Johnson et al.[6]	USA	<1500g, <35 weeks gestation	47,144			Y	Difference in means 15 days		P
Colaizy et al. [33]	USA	<1,500g		24,023	35,699	Y	17 days	Y	S
Renfrew et al.[4]	UK	500-999g		49,518	96,877	Y	Medical 32 days; Surgical 66 days	Y	S
Renfrew et al.[4]	UK	1000-1749g		29,379	57,425	Y	Medical 19 days; Surgical 39 days	Y	S
Renfrew et al. [4]	UK	1750-2500g		44,579	72,625	Y	Medical 35 days; Surgical 55 days	Y	S
Pokhrel et al.[25]*	UK	All		26,797	29,151	Y	27 days	Y	S
Mahon et al. [34*]	UK	All		25,158	27,711	Y	27 days	Y	S
Drane[35]	Australia	1500-1999g		14,469	19,113	N		Y	S
Drane[35]	Australia	<1500g		25,548	49,904	N		Y	S
Total (non-incremental) charges/LOS									
Abdullah et al. [36]	USA	All	233,524	193,851	350,519		Medical median 36 days Surgical median 62 days		P
Zhang et al. [37] All surgical	USA	All			507,811 ± 457,732		Mean 72 days		P
Zhang et al. [37] Small bowel	USA	All			604,526 ± 487,942		Mean 87 days		P
Zhang et al. [37] Large bowel	USA	All			463,267 ± 453,054		Mean 65 days		P
Zhang et al. [37] Small and large bowel	USA	All			531,170 ± 423,001		Mean 79 days		P
Incremental charges/LOS									
Bisquera et al. [38]	USA	<1500g		121,015	305,739		Difference in means Medical 22 days Surgical 60 days	N	P

Abbreviation: LOS: Length of stay

Notes: * Pokhrel et al. and Mahon et al. use the same underlying sources (UK Department of Health Reference Costs and NHS Hospital Episode Statistics) and approach to calculating costs but the data are based on different years. Studies are ordered by country and then by date.



Abbreviations: DM: Donor milk; NEC: Necrotizing enterocolitis

Figure 1. Study selection flow diagram

Supplementary File 1: Full search strategy

Final search criteria 11.10.16 – Donor milk

Medline = 601 hits

1. Human milk.mp. or Milk, Human/
2. donor milk.mp.
3. donor human milk.mp.
4. donor breast milk.mp.
5. Milk Banks/ or milk bank*.mp.
6. 1 or 2 or 3 or 4 or 5
7. cost.mp. or “Costs and Cost Analysis”/
8. economic*.mp.
9. Economics/ or economics.mp.
10. value.mp.
11. Budget.mp. or Budgets/
12. fee.mp. or “Fees and Charges”/
13. Saving.mp. or Income/
14. 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 6 and 14
16. limit 15 to (English language and yr=”1996 –Current”)

EMBASE = 586

1. human milk.mp. or breast milk/
2. donor milk.mp.
3. donor human milk.mp.
4. donor breast milk.mp.
5. milk bank*.mp.
6. 1 or 2 or 3 or 4 or 5
7. "health care cost"/ or cost.mp. or "cost"/ or "cost effectiveness analysis"/ or "hospital running cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/
8. cost analysis.mp.
9. economic*.mp.
10. value.mp.
11. budget/ or budget.mp.
12. fee/ or fee.mp.
13. 7 or 8 or 9 or 10 or 11 or 12
14. 6 and 13
15. limit 14 to (english language and yr="1996 -Current")

CINAHL = 1155

1. human milk
2. donor milk
3. donor human milk
4. donor breast milk
5. milk bank*
6. 1 or 2 or 3 or 4 or 5
7. cost OR price OR expense OR value
8. cost AND analysis
9. economic*
10. budget
11. fee

12. saving
13. 7 or 8 or 9 or 10 or 11 or 12
14. 6 and 13
15. Limit 14 to (english language and yr="1996 -Current")

Final search criteria 25.10.16 – NEC

Medline = 256 hits
1. cost.mp. or "Costs and Cost Analysis"/
2. economic*.mp.
3. Economics/ or economics.mp.
4. value.mp.
5. Budget.mp. or Budgets/
6. fee.mp. or "Fees and Charges"/
7. Saving.mp. or Income/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Necrotising enterocolitis.mp. or Enterocolitis, Necrotizing/
10. NEC
11. 9 or 10
12. 8 and 11
13. limit 12 to (English language and yr="1996 –Current")

EMBASE = 250
1. "health care cost"/ or cost.mp. or "cost"/ or "cost effectiveness analysis"/ or "hospital running cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/
2. cost analysis.mp.
3. economic*.mp.
4. value.mp.
5. budget/ or budget.mp.
6. fee/ or fee.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Necrotising enterocolitis.mp. or Enterocolitis, Necrotizing/
9. NEC
10. 8 or 9
11. 7 and 10
12. limit 11 to (english language and yr="1996 -Current")

CINAHL = 172
1. cost OR price OR expense OR value
2. cost AND analysis
3. economic*
4. budget
5. fee
6. saving
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. NEC
9. necrotising enterocolitis
10. necrotizing enterocolitis
11. 8 OR 9 OR 10
12. 7 AND 11
13. Limit 12 to (english language and yr="1996 -Current")

Supplementary File 2: NEC treatment costs/charges additional study characteristics (cells left blank if data not reported)

Author	Primary (P) /Secondary (S) data	Definition of NEC	Infants included/ excluded	Sample size if primary data	Adjustments for infant characteristics?	Data source(s)
Abdullah et al. (2010)	P	ICD-9: 777.5 plus surgical codes	All infants (results also presented by dead/alive) <60 days old at admission	20,822 NEC cases 5,403 surgical	Y	National Inpatient Sample Kids' Inpatient Database (both Agency for Healthcare Research and Quality), USA
Bartick et al. (2010)	S			N/A	N/A	Extrapolated from Weimer (2001) and Bisquera et al. (2002)
Bisquera et al. (2002)	P	Bells criteria ≥ 2	Alive infants	49 medical NEC + 98 controls; 37 surgical NEC + 74 controls	N	Hospital case notes and charges (2 hospitals in the USA)
Colaizy et al. (2016)	S	Bells criteria ≥ 2	Excluded if died in first 3 days	N/A	Y	Johnson 2013 results, plus 15% overheads + physician fees based on estimated incremental LOS
Drane (1997)	S	Major episode of illness with or without significant operation		N/A	N/A	Australian Department of Health, Housing, Local Government and Community Services 1993
Ganapathy et al. (2012)	P	ICD-9: 777.50–777.53 plus surgical codes	Excluded if died in first 3 days or if daily cost<US$100	259 NEC cases/2,560 82 surgical	Y	California Office of Statewide Health Planning and Development Hospital Discharge data, USA
Johnson et al. (2013)	P	ICD-9: 777.5, 777.52, 777.5, 765.01–765.05, 765.11–765.15	Excluded if died during stay	29 NEC cases/425	Y	Rush University Medical Centre cost database, USA Costs deflated to be national averages
Johnson et al. (2015)	P	Modified Bell's criteria $\geq$ 2. Surgically: peritoneal drain or exploratory laparotomy	Excluded if died during stay	29 NEC cases/291 5 surgical	Y (incremental only)	Rush University Medical Centre cost database, USA
Mahon et al. (2016)	S			N/A	N/A	Costs: UK Department of Health Reference Costs 2011/12 LOS: England Hospital Episode Statistics 2011/12
Pokhrel et al. (2015)	S			N/A	N/A	Costs: UK Department of Health Reference Costs 2009/10 LOS: England Hospital Episode Statistics 2009/10
Renfrew et al. (2009)	S	Bells criteria ≥ 2		N/A	N/A	Costs: UK Department of Health Reference Costs 2007/08 LOS: Bisquera et al. (2002), Stoll et al. (2002), Fanaraff et al. (1998)
Smith et al. (2002)	S	ICD-9: 777.5, 777.8		N/A	N/A	Costs: Australian National Hospital Cost Data Collection 1997/98

Stey et al. (2015)	P	ICD-9: 777.5, 777.51, 777.52, 777.53		101 Peritoneal drainage (PD); 172 PD+Laparotomy; 426 Laparotomy	Y (costs, not LOS)	California Office of Statewide Health Planning and Development Linked Birth File Dataset, USA
Struijs et al. (2012)	P			13 Early closure; 62 Late closure	N	Hospital case notes; Dutch guideline prices for economic evaluations 2004 edition
Weimer (2001)	S			N/A	N/A	Costs/LOS: US Health Care Policy and Research National Inpatient Sample 1996
Wight (2001)	S			N/A	N	Sharp Mary Birch Hospital for Women cost database, USA
Zhang et al. (2011)	P	ICD-9: 777.5 plus surgical codes	<60 days old at admission	5,374 surgical NEC cases; 2,126 short bowel (SB); 963 long bowel (LB); 1,282 SB+LB	N	National Inpatient Sample Kids' Inpatient Database (both Agency for Healthcare Research and Quality), USA

Abbreviations: NEC: necrotizing enterocolitis; lOS: Length of stay.
Please see main text reference list for full references.