Cost-Effectiveness of Supplemental Donor Milk Versus Formula for Very Low Birth Weight Infants

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abstract

OBJECTIVES: To determine the cost-effectiveness of supplemental donor human milk (DHM) versus preterm formula (PTF) for very low birth weight (VLBW, <1500 g) infants from a societal perspective to 18 months' corrected age.

METHODS: This prospective cost-effectiveness analysis of 363 VLBW infants was conducted for a randomized control trial. Infants recruited from October 2010 to December 2012 were fed DHM or PTF whenever mother's milk was unavailable. Formal health care costs for initial hospitalization and readmissions were obtained from standardized cost-accounting systems and physician fees. Informal and nonhealth care sector costs (eg, caregiver transportation, labor market earnings) were calculated from parent reports.

RESULTS: Mean infant birth weight was 996 (SD, 272) grams. Incidence of necrotizing enterocolitis (NEC) differed between groups (all stages 3.9% DHM, 11.0% PTF; $P = .01$). Costs to 18 months did not differ with a mean (95% confidence interval) of 217 624 (197 697–237 551) and 217 245 (196 494–237 995) 2015 Canadian dollars in the DHM and PTF groups. Postdischarge costs were lower in the DHM (46 440 [40 648–52 233]) than PTF group (55 102 [48 269–61 934]) ($P = .04$), driven by parent lost wages. DHM cost an additional $5328 per case of averted NEC.

CONCLUSIONS: In a high mother's milk use setting, total costs from a societal perspective to 18 months of providing supplemental DHM versus PTF to VLBW infants did not differ, although postdischarge costs were lower in the DHM group. Although supplemental DHM was not cost-saving, it reduced NEC supporting its use over PTF.

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WHAT'S KNOWN ON THIS SUBJECT: Supplemental donor human milk (DHM) compared with formula reduces the incidence of necrotizing enterocolitis in very low birth weight infants. The cost-effectiveness of DHM in this population from a societal perspective up to 18 months' corrected age is unknown.

WHAT THIS STUDY ADDS: This is the first prospective cost-effectiveness analysis of supplemental DHM versus formula. It shows costs of supplemental DHM compared with formula for very low birth weight infants did not differ from a societal perspective up to 18 months' corrected age.

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Mother's milk is associated with many positive health outcomes, including a reduction in length of hospital stay, risk of sepsis and necrotizing enterocolitis (NEC), and improved neurodevelopment.[1–7] As many mothers of very low birth weight (VLBW, <1500 g) infants are unable to provide a sufficient volume of their own milk, a supplement is required. Increasingly, the supplement of choice is pasteurized donor human milk (DHM) despite limited data evaluating its cost-effectiveness.

The strongest evidence in support of supplemental DHM is its NEC-protective effect. Meta-analyses of randomized control trials (RCTs) show that using preterm formula (PTF) as a supplement increases the risk ratio of NEC compared with DHM (2.8 [95% confidence interval (CI), 1.4 to 5.5]).[8] In the United States, 1 case of NEC is estimated to increase formal health care sector costs by $30 681 US dollars.[9] Authors of observational studies and modeled estimates suggest that DHM may result in formal health care sector cost-savings compared with PTF, but no study has used prospectively collected infant-level health care costs collected as part of an RCT to evaluate the value-for-money of using DHM as a supplement to mother's milk.[10–12] Accordingly, the aim of this study was to evaluate the cost-effectiveness of DHM versus PTF as a supplement to mother's milk from a societal perspective to 18 months' corrected age (CA).

METHODS

Overview of the Clinical Trial

The Donor Milk for Improved Neurodevelopmental Outcomes (ISRCTN35317141) study was a double-blinded RCT in which 363 VLBW infants were enrolled from tertiary NICUs in southern Ontario between October 2010 and December 2012. The aim of the RCT was to determine if nutrient-enriched DHM compared with PTF as a supplement to mother's milk reduced neonatal morbidity, supported growth, and improved neurodevelopment in VLBW infants. Infants were randomly assigned within 96 hours of birth to receive either supplemental DHM or PTF for 90 days or discharged from the hospital, whichever occurred first. Enteral feeds were initiated on the third postnatal day (interquartile range [IQR] 2–4) and advanced 10 to 25 mL/kg per day up to 160 mL/kg per day.[13] Nutrient fortification of human milk commenced at ≥120 mL/kg per day using bovine-based multinutrient fortifiers. Once fortification of DHM commenced, a protein module was added to bring the estimated protein concentration to that of mature mother's milk. The feeding intervention continued after transfer to community level II NICUs and follow-up of infants continued until 18 months' CA. Baseline demographics and feeding metrics are provided in Table 1. The study protocol and neurodevelopmental, growth and clinical outcomes are published.[13, 14] Research ethics boards at each

TABLE 1 Baseline Characteristics and Clinical Outcomes of VLBW Infants From the RCT

Parameter	PTF (*n* = 182)	DHM (*n* = 181)	*P*
Gestational age (wk) at birth, mean ± SD	27.8 ± 2.7	27.5 ± 2.4	.21
Birth wt (g), mean ± SD	996 ± 272	995 ± 273	.99
Small for gestational age, *n* (%)	24 (13.2)	21 (11.6)	.63
Maternal age (y), mean ± SD	32.6 ± 6.4	31.4 ± 5.9	—
Maternal education, *n* (%)			
High school or less	39 (22.3)	49 (29.0)	—
College or vocational diploma	55 (31.4)	47 (27.8)	—
Baccalaureate	46 (26.3)	46 (27.2)	—
Postbaccalaureate	35 (20.0)	27 (16.0)	—
Mother's milk use in the first 28 d, median (IQR)[a,b]	98.5 (54.6–100.0)	95.5 (61.2–100.0)	.66
Length of feeding intervention, median (IQR), d[b]	60 (43–90)	65 (41–90)	.40
Exclusive mother's milk feeding during intervention, *n* (%)	49 (26.9)	51 (28.2)	.73
Mother's milk use during intervention among supplement users, median (IQR)[a,b]	63.3 (9.6–97.2)	58.4 (13.6–96.0)	.96
Duration of mother's milk use (d), median (IQR)[b]	122 (45–288)	133 (54–245)	.78
Length of hospital stay (d), median (IQR)[b]	67.0 (50.0–102.5)	77.0 (50.5–104.0)	.20
Respiratory support (d), median (IQR)[b]	31.5 (7.2–64.0)	40.0 (10.0–84.0)	.14
Oxygen support at 36 wk, *n* (%)	37 (20.7) *n* = 179	44 (25.1) *n* = 175	.36
Confirmed NEC (stage ≥ I), *n* (%)	20 (11.0)	7 (3.9)	.01
Late-onset sepsis, *n* (%)	35 (19.2)	44 (24.3)	.24
Severe retinopathy of prematurity, *n* (%)	8 (4.4)	7 (3.9)	.80
Death, *n* (%)	20 (11.0)	17 (9.4)	.82

Values are presented as mean ± SD or frequency (%). Categorical data were analyzed by using Cochran–Mantel–Haenszel statistics (controlling for recruitment site), and continuous data were analyzed by using linear regression (controlling for site and birth weight strata [<1000, ≥1000 g] unless indicated). —, not applicable.

[a] Expressed as a percent of all enteral feeds.

[b] Data analyzed by using Mann–Whitney *U* test.

TABLE 2 Comparison of Cost Components of VLBW Infants From Birth to 18 Months' CA From a Societal Perspective

Costs (2015 CAD)	PTF (n = 182)	DHM (n = 181)	P
Total birth to discharge	169 409 (151 138–187 680)	177 085 (158 971–195 200)	.40
Hospital case cost	147 303 (131 210–163 397)	154 710 (138 118–171 302)	.37
Physician	8522 (7874–9171)	8873 (8216–9530)	.42
Enteral feeds	41 (36–47)	921 (741–1100)	<.0001
Caregiver expenses	15 404 (12 009–18 800)	13 801 (11 768–15 835)	.15
Productivity losses	12 148 (9019–15 277)	10 223 (8507–11 939)	.23[a]
Household help	94 (18–169)	163 (63–264)	.52[a]
Child care	164 (68–260)	278 (116–439)	.67[a]
Accommodation	160 (27–293)	202 (87–317)	.64[a]
Meals	949 (754–1144)	1 036 (796–1276)	.78[a]
Breast pump	267 (229–305)	261 (228–293)	.58[a]
Travel	1505 (1291–1718)	1530 (1321–1740)	.74[a]
Other	14 (5–23)	26 (0–60)	.47[a]
Total postdischarge to 18 mo CA	55 102 (48 269–61 934)	46 440 (40 648–52 233)	.04[a]
Re-hospitalization	6050 (2951–9148)	6632 (4140–9123)	.80[a]
Visits to health care professional	2389 (1837–2942)	2405 (1922–2888)	.72
Medication	63 (45–81)	52 (41–63)	.27[a]
Visits to emergency department	75 (59–91)	75 (59–91)	.80[a]
Visits to walk-in clinic	69 (52–86)	89 (67–111)	.22[a]
Visits to follow-up clinic	738 (700–776)	723 (686–759)	.76[a]
Productivity losses	45 720 (39 559–51 881)	36 467 (30 918–42 016)	.03[a]
Total birth to 18 mo CA	217 245 (196 494–237 995)	217 624 (197 697–237 551)	.74

Costs are presented as mean (95% CI). Cost differences (total and component) between groups were analyzed by GEE adjusted for clustering at recruitment site and birth weight strata (<1000, ≥1000 g) unless indicated otherwise.

[a] Costs between groups were analyzed by nonparametric regression analyses.

participating hospital approved the study.

Cost-effectiveness Analysis

Cost-effectiveness analysis from a societal perspective was planned a priori and conducted alongside the RCT.[15,16] The RCT sample size was established to detect a 5-point difference in mean cognitive composite scores on the *Bayley Scales of Infant and Toddler Development, Third Edition* (Bayley-III) between infants randomly assigned to the DHM versus PTF group, the primary outcome.[13,14] As reported, we found no difference in Bayley-III cognitive composite scores between feeding groups (adjusted scores 92.9 in DHM versus 94.5 in PTF groups; fully adjusted mean difference, −2.0 [95% CI, −5.8 to 1.8]).[14] We did find a significant reduction in NEC stage ≥ II among infants randomly assigned to the DHM (1.7%) versus PTF (6.6%) group (risk difference of −4.9% [95% CI, −9.0 to −0.9; P = .02]). The primary cost-effectiveness analysis in this manuscript, then, was conducted with a time horizon of birth to 18 months' CA as intended a priori but focuses on the prevention of NEC rather than improvement in neurodevelopment. In secondary analyses, costs with a birth to hospital discharge time horizon were assessed in terms of total formal and informal health care and nonhealth care costs and cost-effectiveness in preventing NEC. Given the low incidence of NEC stage ≥ II, we used NEC stage ≥ I in these analyses, defined as demonstrating clinical symptoms according to Bells criteria followed by treatment involving suspension of enteral feeds and antibiotics for a minimum of 7 days.[14,17] A secondary analysis of costs postdischarge to 18 months' CA was also included. Since the study's completion, the Second Panel on Cost-Effectiveness in Health and Medicine recommended that in addition to presenting results from a societal perspective, they be presented from a health care sector perspective.[18] Cost-effectiveness analysis from a health care sector perspective include formal health sector costs (medical) costs whether paid by a third-party or out-of-pocket by caregivers, whereas from a societal perspective includes all costs and health effects regardless of who incurred them or obtained the health effects. The cost components included in each reference case perspective are summarized in Supplemental Table 5 and costs from a health care sector perspective can be calculated from the tables summarizing component costs (Table 2, Supplemental Tables 6 and 7).

Estimation of Cost Components

Formal health care sector medical costs incurred for each infant during their initial hospital stay were secured from the finance departments of all tertiary NICUs where >80% of initial hospitalization costs occurred and 12 of 17 community NICUs. Hospitals in the province of Ontario, Canada follow a standardized

costing methodology developed by the Ontario Case Costing Initiative (OCCI).[19] Formal health care medical costs captured in this system include expenditures associated with professional salaries (eg, nursing and other allied health but not physician), surgery, laboratory services, diagnostic imaging, and pharmacy. Indirect costs incurred by institutions, such as administration, human resources, and plant operations were allocated to each infant based on length of stay. Infant-specific health care costs were unavailable from 5 participating community NICUs because the OCCI standardized accounting system was not fully implemented. For these centers, a per diem cost was imputed by using mean costs calculated from the other 12 community NICUs, matching for the infant's gestational age at birth to the nearest week.

Physician costs, not captured as part of OCCI, were calculated by using Ontario fee schedules.[20] Costs of enteral feeds were calculated by applying DHM, fortifier, and formula unit prices to volumes and recipes of feeds recorded daily. The unit cost of DHM used in our analysis was $4.95 Canadian dollars (CAD) per ounce; the cost of DHM purchased for the study adjusted to 2015 CAD. At the time of the study, most participating hospitals received fortifier and formula free of charge from vendors. To capture costs from a societal perspective, we used the price for formula and fortifier paid by 1 of our community NICUs participating in the Baby Friendly Initiative.[21] The cost of bovine-based PTF, for example, was $0.13 CAD per ounce. The cost to fortify one ounce of human milk was $0.14 CAD per ounce.

A standardized Family Health Economic Questionnaire, previously employed by the investigators, was used to calculate caregiver informal health sector and nonhealth sector costs, including transportation to the hospital, meals away from home, and labor market earnings lost.[22,23]

This questionnaire was completed monthly by parents from the time of birth up to 18 months' CA when either visiting their child in the NICU or by telephone with research staff.

Family Health Economic questionnaires were also used to capture the frequency of re-hospitalizations, medical or follow-up clinic visits, health care professional visits, prescription and over-the-counter medications, as well as reported loss of caregivers' labor market earnings. Physician and other health care professional costs incurred postdischarge were calculated by using the province of Ontario fee schedules.[20] If an appropriate fee schedule was unavailable, costs were estimated by using average provincial wages posted on regulatory college and government Web sites. Costs of medications were assigned by using provincial reimbursement rates.[24] Costs of re-hospitalization were calculated based on the mean cost per episode, as defined by the principal reason for admission by using the OCCI database.[19]

If families were unavailable by telephone after discharge to complete the questionnaire, they were approached at their infant's routine neonatal follow-up visits at 4, 8, 12, and 18 months' CA. In situations in which Family Health Economic questionnaires were incomplete, a mean per diem cost for the infant was imputed based on the mean costs from infants with complete data matched by family's income. At least some costing data were available on all infants in the study. Formal health care sector (medical) costs not requiring any imputation for missing days were available for 240 infants for their entire initial hospitalization and 361 for their tertiary NICU stay (Supplemental Fig 3). Complete cost data not requiring imputation were available for 223 infants from birth to 18 months' CA.

Statistical Analyses

Statistical analyses were conducted by using SAS Version 9.4 (SAS Institute, Inc, Cary, NC) using an intent-to-treat approach. All statistical tests were 2-tailed and $P < .05$ was considered statistically significant. Costs are reported in 2015 CAD. In 2015, 1.00 CAD was equivalent to 0.78 US dollars. Comparisons of clinical outcomes between groups were conducted by using Cochran–Mantel–Haenszel statistics with adjustment for site for categorical variables. For continuous outcomes, linear regression statistics adjusted for recruitment site and birth weight stratum (<1000 or ≥1000 g) or Wilcoxon rank tests for nonnormally distributed data were conducted.

Comparison of log-transformed mean total and cost components between groups were performed by using generalized estimating equation (GEE) adjusting for repeated measures taken at the same recruitment site and birth weight stratum. For comparing individual expense categories with a large number of 0 values (eg, hospital readmissions), repeated-measures nonparametric modeling (PROC MIXED, SAS) was used.

To assess sampling uncertainty in estimates of cost-effectiveness, we randomly sampled 1000 times with replacement all 363 subjects in the original data set to obtain 363 pairs of costs and effects (eg, NEC). For each of the 1000 samples, the mean costs and effects were plotted (eg, Fig 1) and the incremental cost-effectiveness ratio (iCER) was calculated. Specifically, iCER

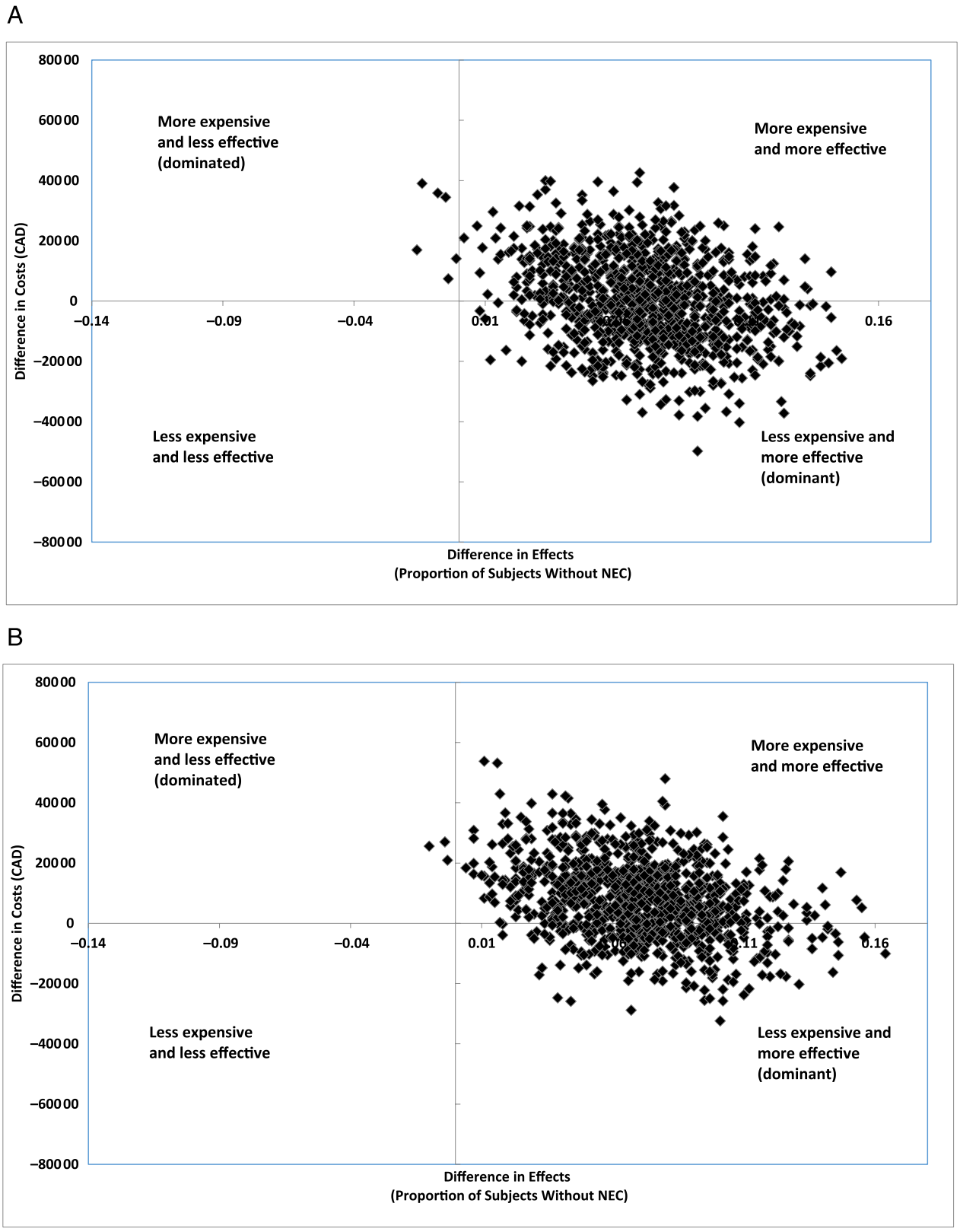

FIGURE 1

Scatterplot showing differences in mean costs and effects (NEC) between DHM and PTF groups using the following: (A) a birth to 18 months' CA and (B) a birth to discharge time horizon. Each point represents 1 simulated cohort or bootstrap replication, as described in the text. Most of the 1000 points are on the northeast and southeast quadrants of the graph, indicating that although supplemental DHM was more effective at reducing NEC than PTF, there was no clear difference in cost.

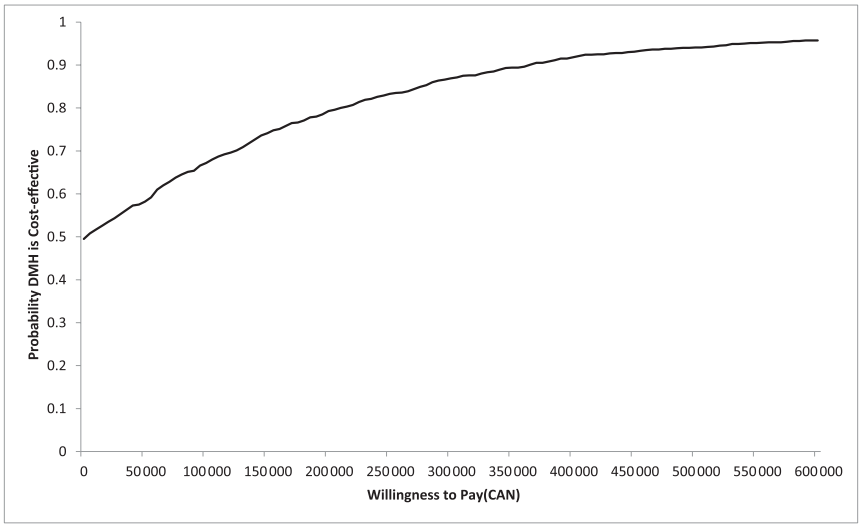

FIGURE 2
CEAC for DHM compared with PTF by using a birth to 18 months' CA time horizon. The curve shows the proportion of bootstrap replications in which the cost-effectiveness of DHM was at or below the willingness-to-pay thresholds on the horizontal axis. This corresponds to the probability that the therapy would be economically desirable to decision-makers with those thresholds.

is the difference in the mean total cost between infants randomly assigned to the DHM and PTF groups divided by the difference in mean effectiveness (eg, NEC) between groups. We report sampling uncertainty using a cost-effectiveness acceptability curve (CEAC) (Fig 2),[25,26] which illustrates the probability that the intervention would be cost-effective given a willingness-to-pay threshold from $0 to $600 000 per case of NEC prevented.

Parameter uncertainty was assessed by using sensitivity analyses, in which the cost components were calculated first excluding infants who received exclusively mother's milk during the intervention (Supplemental Table 6) and second excluding infants who had incomplete Family Health Economic questionnaires (Supplemental Table 7). Additional sensitivity analyses included calculation of the iCER using a range of plausible costs for DHM ($3.00–$7.60 per ounce), formal health care sector medical costs (initial and readmission), physician fees from birth to 18 months' CA (70%–130%), and caregiver wages to reflect the Ontario minimum wage and national Canadian wage,[27,28] and NEC stage ≥ II instead of NEC stage ≥ I as the health outcome (Table 3).

RESULTS

Detailed description of progress of infants through the trial and clinical outcomes were previously published.[14] Briefly, of 363 infants enrolled, the mean ± SD gestational age and weight at birth was 27.7 ± 2.6 weeks and 996 ± 272 g, respectively (Table 1). Infants born <1250 g comprised 75.8% (n = 275) of those enrolled and 12.4% (n = 45) were born small for gestational age. No statistically significant differences were found between infants randomly assigned to the DHM and PTF group with respect to the number of days they remained in the feeding intervention or mother's milk use (Table 1). As previously reported, there were no statistically significant differences between infants randomly assigned to the DHM versus PTF group in adjusted composite cognitive (92.9

TABLE 3 Deterministic Sensitivity Analyses for the Cost-effectiveness Ratio From Birth to 18 Months' CA From a Societal Perspective

	Parameter	Incremental Cost	iCER (% Dominant)
Cost	Base case analysis (n = 363)	379	5328 (47.9)
	Hospital and physician fees (birth to discharge)		
	Increased by 30%	2707	38 005 (42.7)
	Decreased by 30%	−1948	−27 350 (56.8)
	Hospital and physician fees (birth to 18 mo CA)		
	Increased by 30%	2878	40 409 (43.7)
	Decreased by 30%	−2119	−29 753 (56.4)
	DHM (CAD per ounce)		
	$3.00	−401	−5632 (49.2)
	$4.00	225	3159 (51.8)
	$6.00	534	7496 (47.4)
	$7.60	3036	42 636 (44.8)
	Hourly wage		
	2015 national average: $27.59	8692	122 053 (29.2)
	2015 Ontario minimum: $11.25	9238	129 721 (21.0)
Effect	NEC stage ≥ II[a]	379	7687 (48.9)

[a] The cost-effectiveness ratio was calculated in relation to NEC stage ≥II instead of NEC of any stage.

[95% CI, 89.8 to 95.9] and 94.5 [91.4 to 97.5]), language (87.3 [95% CI, 83.8 to 90.8] and 90.3 [95% CI, 86.7 to 93.9]), motor (91.8 [95% CI, 88.8 to 94.9] and 94.0 [95% CI, 91.0 to 97.0]) scores on the Bayley-III at 18 months' CA. There were no differences in major clinical outcomes during initial hospitalization except for the incidence of NEC.

TABLE 4 The iCER, Calculated by Using a Birth to 18 Months' CA Time Horizon and a Societal Perspective

Intervention	Mean Cost, CAD	ΔC	Proportion of Cases of NEC, E	ΔE	iCER, ΔC/ΔE
DHM (n = 181)	217 624	379	0.03867	0.07122	5328
PTF (n = 182)	217 245	—	0.10989	—	

—, not applicable.

Comparison of Total and Cost Components

Considering all randomly assigned infants, mean total cost accrued from a societal perspective from birth to 18 months' CA in the DHM group was $217 624 ($197 697–$237 551) and did not differ statistically from $217 245 ($196 494–$237 995) in the PTF group (P = .74) (Table 2). Likewise, infants randomly assigned to the DHM and PTF group had similar total initial hospitalization costs (P = .40). Examination of postdischarge to 18 months' CA costs revealed lower costs for infants randomly assigned to the DHM versus PTF group (P = .04). Postdischarge, caregivers of infants randomly assigned to the DHM group had significantly lower productivity losses than infants randomly assigned to the PTF group (P = .03).

Cost-effectiveness and Associated Uncertainty

Using an 18-month time horizon, cost-effectiveness analysis revealed that DHM cost slightly more on average and had higher effectiveness (Table 4). Figure 1 illustrates the distribution of the differences in costs and effects between treatment groups using either a birth to 18-month time horizon (Fig 1A) or birth to discharge time horizon (Fig 1B) in which each point on the graphs represents a single bootstrap replication. As shown, a preponderance of replications in both figures are found on the right side indicating DHM was, on average, protective against NEC. In addition, Fig 1A reveals a 52.1% chance that DHM was more expensive using an 18-month time horizon. When the time horizon was restricted to initial hospitalization, there was a 71.7% chance that DHM was more costly and more effective in reducing NEC and a 28.0% chance that DHM would result in cost-savings and be more effective (ie, "dominant").

Examination of the CEAC, however, reveals broad uncertainty in the estimation of the cost-effectiveness ratio (Fig 2). The CEAC shows the probability that an intervention is acceptable at various thresholds of willingness to pay for an outcome. There is a 67% probability that the therapy is acceptable to a decision-maker with a threshold of $100 000 per case of NEC prevented. Using a threshold that is analogous to the traditional upper limit of a CI, there is a 95% probability that DHM would be acceptable to a decision-maker whose threshold is $540 000 per case of NEC prevented.

Deterministic Sensitivity Analyses

Calculated total costs and iCER estimates were sensitive to hospitalization costs, physician fees, and the cost of DHM and caregiver wages (Table 3). If hospitalization and physician fees from birth to 18 months' CA were reduced to 70% of the base case estimate, DHM would result in a mean cost-savings of $2119. Similarly, when the unit price of DHM was decreased to $3.00 per ounce, DHM would result in lower costs compared with PTF. In a separate sensitivity analysis, we re-ran the cost comparison analyses in the sample of infants with complete cost data to 18 months' CA (n = 223, Supplemental Table 7). As illustrated, total costs from birth to 18 months' CA remain similar between groups.

DISCUSSION

In this prospective cost-effectiveness analysis conducted for a RCT, the total costs of using DHM as a supplement to mother's milk did not differ from PTF from a societal perspective to 18 months' CA. Our data suggest that it would cost ~$5328 (2015 CAD) per case of NEC averted to provide supplemental DHM; however, it should be emphasized that there was broad uncertainty around this estimate. In fact, formal analysis of this uncertainty suggests that there is only a 48% probability that DHM was simultaneously more effective and less costly than PTF in preventing NEC using a birth to 18-months' CA time horizon (Fig 1A), and only a 67% probability that the intervention would be acceptable to decision-makers who were willing to spend $100 000 to prevent one case of NEC.

Interestingly, when comparison of total costs was restricted to postdischarge, there was a statistically significant cost advantage of using DHM as a supplement (Table 2). However, this difference was no longer statistically significant in sensitivity

analyses in which exclusively mother's milk-fed infants were removed (Supplemental Table 6). The difference in the base case analysis appeared to be mediated by lower productivity losses as a result of caring for their infant. Because there were no differences in the number of visits to health care professionals or hospital readmissions between treatments, we speculate that infants in the PTF group may have been slightly more fragile, requiring a parent to stay home from work but not so ill they required incrementally more medical attention.

Our findings differ from estimates of cost-savings associated with using DHM instead of PTF reported in the literature.[10–12] Arnold[10,11] suggested potential cost-savings associated with DHM in both a case study of a formula-intolerant preterm infant with severe bronchopulmonary dysplasia whose mother was unable to provide breast milk and, in a second paper, using 3 modeling exercises based on assumptions of reduction in length of stay and of NEC. Similarly, Wight[12] estimated direct hospital cost-savings of supplemental DHM versus PTF for VLBW infants using published clinical findings from a single-site RCT and actual cost-estimates of different components of care from a different center.[29] DHM was assumed to be as effective as mother's milk compared with PTF in preventing NEC and sepsis and shortening length of stay; DHM was not studied in this trial. In 2 other retrospective studies, authors also showed cost-saving associated with the use of human milk-based milk fortifiers to achieve an exclusive human milk diet.[30,31] Although the aforementioned cost-estimates spurred interest in DHM research and helped to engage administrators in a discussion of the merits of DHM, the risk of bias associated with these modeling and retrospective approaches is high and does not consider all costs associated with preterm birth.

There are a number of strengths of the current study. This is the first prospective cost-effectiveness analysis of DHM alongside a blinded RCT, and involved comprehensive analysis of infant-level costs. This experimental approach to health policy minimizes bias, optimizes internal validity, and permits simultaneous consideration of actual cost and effect distributions without the assumptions inherent in modeling studies. Moreover, unlike most formal economic evaluations in the neonatal trial literature, this analysis took a societal perspective, in which an attempt was made to capture all costs related to preterm birth to 18 months' CA, including parental out-of-pocket expenses. In addition to being significant contributors to the validity of our cost estimates, the measurement of such costs highlights the high financial burden accruing to parents of preterm infants in general.

Despite the substantial protections against bias, certain limitations must be acknowledged. First, our study was undertaken in a single Canadian urban area, and the extent to which the results are generalizable to other settings in which mother's milk feeding or costs might differ is uncertain. Of note, sensitivity analysis does show that the cost advantage postdischarge for DHM is not significant when exclusively mother's milk-fed infants were removed from consideration, although there were minimal changes seen with other sensitivity analyses. A second limitation concerns the reliance on caregivers to recall out-of-pocket expenses and certain other health resource use; however, the monthly questionnaire administration is much more frequent than most other prospective economic evaluations in the neonatology literature, and would likely have minimized this problem.

CONCLUSIONS

In a high mother's milk use setting, total costs from a societal perspective to 18 months' CA of providing DHM as a supplement compared with PTF did not differ. Although the total costs were similar, supplemental DHM reduced the risk of NEC compared with supplemental PTF. Given the short- and long-term sequelae associated with NEC, and an additional cost of only $5328 per case of NEC averted, use of DHM over PTF as supplement is justified. Given the observation of cost-savings after hospital discharge associated with supplemental DHM, further exploration of the impact of early supplemental feeding on health outcomes and family costs after discharge is warranted.

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ABBREVIATIONS

Bayley-III: *Bayley Scales of Infant and Toddler Development, Third Edition*
CA: corrected age
CAD: Canadian dollars
CEAC: cost-effectiveness acceptability curve
CI: confidence interval
DHM: donor human milk
GEE: generalized linear modeling
iCER: incremental cost-effectiveness ratio
IQR: interquartile range
NEC: necrotizing enterocolitis
OCCI: Ontario Case Costing Initiative
PTF: preterm formula
RCT: randomized control trial
VLBW: very low birth weight

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REFERENCES

1. Victora CG, Bahl R, Barros AJ, et al; Lancet Breastfeeding Series Group. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet*. 2016; 387(10017):475–490
2. Kim J, Unger S. Human milk banking. *Paediatr Child Health*. 2010;15(9):595–602
3. O'Connor DL, Jacobs J, Hall R, et al. Growth and development of premature infants fed predominantly human milk, predominantly premature infant formula, or a combination of human milk and premature formula. *J Pediatr Gastroenterol Nutr*. 2003;37(4):437–446
4. Patel AL, Johnson TJ, Engstrom JL, et al. Impact of early human milk on sepsis and health-care costs in very low birth weight infants. *J Perinatol*. 2013;33(7):514–519
5. Schanler RJ, Lau C, Hurst NM, Smith EO. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. *Pediatrics*. 2005;116(2):400–406
6. Vohr BR, Poindexter BB, Dusick AM, et al; National Institute of Child Health and Human Development National Research Network. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. *Pediatrics*. 2007;120(4). Available at: www.pediatrics.org/cgi/content/full/120/4/e953

7. Vohr BR, Poindexter BB, Dusick AM, et al; NICHD Neonatal Research Network. Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. *Pediatrics*. 2006;118(1). Available at: www.pediatrics.org/cgi/content/full/118/1/e115
8. Quigley M, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database Syst Rev*. 2014;(4):CD002971
9. Johnson TJ, Patel AL, Bigger HR, Engstrom JL, Meier PP. Cost savings of human milk as a strategy to reduce the incidence of necrotizing enterocolitis in very low birth weight infants. *Neonatology*. 2015;107(4):271–276
10. Arnold LDW. Cost savings through the use of donor milk: case histories. *J Hum Lact*. 1998;14(3):255–258
11. Arnold LD. The cost-effectiveness of using banked donor milk in the neonatal intensive care unit: prevention of necrotizing enterocolitis. *J Hum Lact*. 2002;18(2):172–177
12. Wight NE. Donor human milk for preterm infants. *J Perinatol*. 2001;21(4):249–254
13. Unger S, Gibbins S, Zupancic J, O'Connor DL. DoMINO: donor milk for improved neurodevelopmental outcomes. *BMC Pediatr*. 2014;14:123
14. O'Connor DL, Gibbins S, Kiss A, et al; GTA DoMINO Feeding Group. Effect of supplemental donor human milk compared with preterm formula on neurodevelopment of very low-birth-weight infants at 18 months: a randomized clinical trial. *JAMA*. 2016;316(18):1897–1905
15. Glick HA, Doshi JA, Sonnad SS, Polsky D. *Handbooks in Health Economic Evaluation: Economic Evaluation in Clinical Trials*. 2nd ed. Oxford, United Kingdom: Oxford University Press; 2015
16. Ramsey SD, Willke RJ, Glick H, et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. *Value Health*. 2015;18(2):161–172
17. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg*. 1978;187(1):1–7
18. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA*. 2016;316(10):1093–1103
19. Ontario Ministry of Health and Long Term Care. Health data branch web portal. Available at: https://hsim.health.gov.on.ca/HDBPortal/. Accessed June 15, 2016
20. Ontario Ministry of Health and Long Term Care. Schedule of benefits. Physician services under the health insurance act. Available at: www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20151221.pdf. Accessed July 15, 2016
21. Baby Friendly Initiative. Baby-friendly initiative Ontario. Available at: www.bfiontario.ca/. Accessed July 15, 2016
22. Dukhovny D, Dennis CL, Hodnett E, et al. Prospective economic evaluation of a peer support intervention for prevention of postpartum depression among high-risk women in Ontario, Canada. *Am J Perinatol*. 2013;30(8):631–642
23. Mowitz ME, Zupancic JA, Millar D, et al. Prospective economic evaluation alongside the non-invasive ventilation trial. *J Perinatol*. 2017;37(1):61–66
24. Ontario Ministry of Health and Long Term Care. Ontario drug benefit e-formulary. Available at: www.health.gov.on.ca/en/pro/programs/drugs/odbf_eformulary.aspx. Accessed July 15, 2016
25. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ*. 2001;10(8):779–787
26. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves—facts, fallacies and frequently asked questions. *Health Econ*. 2004;13(5):405–415
27. Government of Canada. Hourly minimum wages in CANADA for adult workers. Available at: http://srv116.services.gc.ca/dimt-wid/sm-mw/rpt2.aspx. Accessed February 28, 2017
28. Statistics Canada. Average hourly wages of employees by selected characteristics and occupation, unadjusted data, by province (monthly). Available at: www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/labr69g-eng.htm. Accessed February 25, 2017
29. Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. *Pediatrics*. 1999;103(6 pt 1):1150–1157
30. Ganapathy V, Hay JW, Kim JH. Costs of necrotizing enterocolitis and cost-effectiveness of exclusively human milk-based products in feeding extremely premature infants. *Breastfeed Med*. 2012;7(1):29–37
31. Assad M, Elliott MJ, Abraham JH. Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet. *J Perinatol*. 2016;36(3):216–220

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