

Institution: University of York		
Unit of Assessment: 2 - Public Health, Health Services and Primary Care		
Title of case study: Evidence-based enteral feeding practices for very preterm or very low birth weight infants.		
Period when the underpinning research was undertaken: 2008-2019		
Details of staff conducting the underpinning research from the submitting unit:		
Names:	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
William McGuire Jennifer Brown	Professor Research fellow	2008- present 2011- present
Period when the claimed impact occurred: 01 August 2013- 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		
<p>1. Summary of the impact (indicative maximum 100 words) University of York research on enteral feeding for very preterm or very low birth weight (VLBW) infants has informed national and international guidelines, influenced policy and practice, and underpinned initiatives to improve care and outcomes globally. Our work is cited as evidence for the use of donor human milk and progressive enteral feeding to reduce necrotising enterocolitis and severe infection and sepsis, optimise growth, and improve long-term outcomes in very preterm or VLBW infants. These benefits are associated with substantial cost savings by reducing the duration of hospitalisation and resource use in the long-term.</p>		
<p>2. Underpinning research (indicative maximum 500 words) One-in-fifty infants is born “very preterm” (< 32 weeks’ gestation) or VLBW (< 1,500g). The commonest causes of morbidity and late-neonatal mortality in this vulnerable population are necrotising enterocolitis (intestinal inflammation and failure), and bloodstream infection and sepsis. These conditions affect about 20% of very preterm or VLBW infants and are associated with neuro-disabilities requiring life-long care and support.</p> <p>Enteral feeding strategies such as 1) the type of milk that infants receive (human milk versus cow milk-formula) and 2) how and when it is given (since very preterm infants do not regulate their own intake), are major modifiable risk factors for necrotising enterocolitis, infection and sepsis. High-quality evidence is needed to guide policy and practice to improve care and outcomes for very preterm or VLBW infants and their families.</p> <p>With NIHR support since 2013, McGuire, Brown, and colleagues at York’s Centre for Reviews and Dissemination, have led a programme of work to generate a suite of Cochrane systematic reviews that have synthesised the evidence-base for the key feeding and nutritional interventions for very preterm or VLBW infants:</p> <p>Donor human milk: Our meta-analysis of 11 randomised controlled trials (RCTs) showed that feeding with donor human milk rather than cow milk-formula (when sufficient maternal milk is not available) halved the risk of necrotising enterocolitis [B]. Feeding with donor human milk, which typically contains less energy and protein than cow milk-formula, was associated with slower growth. Our review of 14 RCTs showed that human milk enriched with ‘multi-nutrient fortifier’ increased growth rates to recommended levels. Meta-analysis, furthermore, provided clinicians and families with reassurance that fortifying human milk was not associated with a rebound increase in the risk of necrotising enterocolitis [D].</p> <p>Timing of introduction and advancement of enteral feeds: Our Cochrane reviews refuted the long-established practice of ‘conservative’ enteral feeding for very preterm or VLBW infants [A][C][E]. Historically, concern existed that ‘progressive’ enteral feeding (early introduction of milk feeds, and rapid advancement of feed volumes) might stress the immature gastrointestinal tract sufficiently to cause necrotising enterocolitis, infection and sepsis. Our meta-analyses of 28 RCTs (> 5,600 participants) showed that (i) early exposure to small volumes of enteral milk [A] and advancing enteral feeds within the first few days after birth [C] was feasible and was well-tolerated by very preterm or VLBW infants, and that (ii) rapid advancement of feed volumes was</p>		

safe for even the smallest and most fragile infants, and was associated with a reduction in the risk of bloodstream infection and sepsis [E]. This review included data from 2,800 infants who participated in the UK multi-centre RCT of different rates of enteral feeding (co-led by McGuire), the largest trial to-date in this population [F].

3. References to the research (indicative maximum of six references)

(All peer reviewed, all funded by NIHR)

A. Morgan J, Bombell S, **McGuire W.** (2013) 'Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants' Cochrane Database Syst Rev 3:CD000504 [doi.org/10.1002/14651858.CD000504.pub4].

B. Quigley M, **McGuire W.** (2014) 'Formula versus donor breast milk for feeding preterm or low birth weight infants' Cochrane Database Syst Rev 4:CD002971 [doi.org/10.1002/14651858.CD002971.pub3].

C. Morgan J, Young L, **McGuire W.** (2014) 'Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants' Cochrane Database Syst Rev 12:CD001970 [[doi:10.1002/14651858.cd001970.pub5](https://doi.org/10.1002/14651858.cd001970.pub5)].

D. Brown JV, Embleton ND, Harding J, **McGuire W.** (2016) 'Multi-nutrient fortification of human milk for preterm infants' Cochrane Database Syst Rev 5:CD000343 [doi.org/10.1002/14651858.cd000343.pub3].

E. Oddie S, Young L, **McGuire W.** (2017) 'Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants' Cochrane Database Syst Rev 8:CD001241 [doi.org/10.1002/14651858.CD001241.pub7].

F. SIFT Investigators Group (2019) 'Controlled trial of two incremental milk-feeding rates in preterm infants' N Engl J Med 381: pp.1434-1443 [doi.org/10.1056/NEJMoa1816654]. Data first published in: Pediatric Academic Societies Annual Meeting; May 6-9, 2017; San Francisco, CA.

4. Details of the impact (indicative maximum 750 words)

Impact on policy statements, guidelines, toolkits and care pathways

Research undertaken at York has informed international and national guidelines on enteral feeding strategies for very preterm and VLBW infants.

Three sets of World Health Organisation (WHO) guidelines cite York research:

- "Donor Human Milk for Low Birth Weight Infants";
- "Feeding of Very Low Birth Weight Infants"; and
- "Standard Formula for Low Birth Weight Infants".

All are subsets of the WHO's guidance on feeding of low birth weight infants [1].

Research output [B] is cited as the underpinning evidence for recommending that VLBW infants "who cannot be fed mother's own milk should be fed donor human milk [in] settings where safe and affordable milk-banking facilities are available or can be set up". Seven outputs authored by McGuire (including [D][E][F]) are cited as informing feeding guidelines for VLBW infants, including specific recommendations on the rate of enteral feeding and the use of nutrient fortifiers.

York research is cited in other national and international guidelines and policy documents by the American Academy of Pediatrics (AAP), the Canadian Consensus Group (CCG), and the European Association of Perinatal Medicine (EAPM) [2]:

- The AAP 2017 policy statement cites output [B] in recommending the use of donor human milk: "recent studies support health benefits for its use in [VLBW] infants, especially in decreasing rates of necrotizing enterocolitis".
- The CCG 2015 guidelines refer to output [E] to underpin key recommendations for VLBW infants, including to "start trophic feeds preferably within 24h of life"; and "...if the feeds are tolerated for around 2-3 days, consider increasing faster".

- The EAPM 2017 consensus guidelines recommend early initiation of human milk feeds, and their rapid advancement, for VLBW infants, stating that “*there is no evidence of increased NEC [necrotising enterocolitis] with early initiation of feeds or advancing feeds more rapidly*”, based on McGuire’s finding [C][E]. Output [B] is cited to support the recommendation that “*donor breast milk is better than formula as it reduces the risk of necrotising enterocolitis*”.

Impact on training and education

Through its underpinning of WHO and other guidance and policy statements, York research has informed training and education in enteral feeding for very preterm and VLBW infants in the UK and internationally, leading to the wider use of donor human milk and progressive enteral feeding. For example:

- The Interpractice 21st project (Oxford Maternal and Perinatal Health Institute) provides training for healthcare professionals to promote the best international standards in nutrition for preterm infants. The online module, “Feeding Recommendations for the Routine Care of Preterm Infants”, available in English, Spanish, Italian, Russian and Portuguese, cites output [E] as the evidence for recommendations on the initiation, advancement, and volume and frequency of enteral feeds [3].
- The European Standards of Care for Newborn Health, a practical standards-based resource for neonatal healthcare practitioners, cites outputs [B][C][E] in its advice on establishment of enteral feeding in preterm infants [4].

Impact on adoption and practice

The volume and use of donor human milk, and establishment of donor milk banks, has increased substantially in the UK and internationally during the past decade [5]. For example, Human Milk Banking Association of North America data indicate an expansion from 16 non-profit milk banks in 2013 to 30 as of 2020. Collectively, these processed about 85,000L of milk in 2013, rising to ~210,000L in 2019 [5]. The expansion is predicated on research including the York Cochrane reviews, and the WHO guidance that draw on these. Milk banks internationally base their existence and practice on the WHO guidance, as evidenced in sources such as the Australian Government’s healthcare resource pages, and official recommendations for the adoption of milk banks in Spain which cite both the recent WHO guidance and York research [5]. The Health Scotland 2017 report for NHS practitioners and policy makers notes that “*access to donor breast milk in all neonatal units has resolved some of the issues of making breast milk equally available to all babies who need it*” [5].

Further evidence of impact in neonatal care facilities is provided by recent studies in North America. A quality improvement project in Massachusetts (USA) that examined the effect of newly-introduced feeding regimens on growth for very preterm infants cites outputs [C] and [E] as underpinning two of its key elements: “*earlier initiation of trophic feeds [and] accelerated daily feeding*” [6]. A study examining the expansion in US neonatal units using donor human milk for supplemental feeding of very preterm or VLBW infants (74% increase since 2011) cited output [B] as the unpinning evidence that allowed practitioners to become more confident in recommending adopting this practice [7a].

Impact on patient outcomes and cost savings

The changes in practice based on York research have improved care and outcomes for very preterm and VLBW infants. The Massachusetts initiative concluded that the new enteral feeding regimens reduced time to establish feeds and reduced central vascular catheter use, a major risk factor for infection and sepsis in very preterm infants [6]. Another US study showed that “*a progressive standardized, evidence-based feeding protocol was associated with improved growth without increased risk for necrotizing enterocolitis*” in VLBW infants [7b]. In the UK, the Human Milk Foundation, a charitable umbrella organisation for NHS milk banks, connects increased use of donor human milk with reduction in necrotising enterocolitis and the saving of preterm infants’ lives [5].

Cost savings may be associated with adopting enteral feeding regimens informed by the York reviews [8]. The Massachusetts study concluded that “*the change in practice also resulted in cost savings*” because infants spend a shorter time spent in neonatal intensive care units [6]. Economic modelling from a UK NHS perspective suggests that interventions to reduce the use of formula for feeding preterm infants are likely to achieve substantial cost savings for the UK NHS (lifetime quality-adjusted life year gain >10,000), principally by reducing rates of necrotising enterocolitis, sepsis, and neurodevelopmental impairment [9]. In Southern Africa, analysis suggests that donor human milk is a highly cost-effective intervention for very preterm infants, costing (“worst case”) USD619 per Disability Adjusted Life Year averted. This analysis concluded that there is a “*compelling argument to increase the supply of donor milk in middle-income countries*” [10].

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. (a) [World Health Organization e-Library of Evidence for Nutrition Actions](#). (b) Letter of support from World Health Organization.
2. **Collected guidance and policy statements:** [American Academy of Pediatrics Policy statement](#); [European Association of Perinatal Medicine Consensus Guidelines](#); [Canadian Consensus Group Guidelines for Feeding Very Low Birth Weight Infants](#)
3. Interpractice-21st programme of the Oxford Maternal and Perinatal Health Institute, module 3.
4. [The European Standards of Care for Newborn Health](#)
5. Websites and other information relating to specific milk banks: [Scottish Government announcement of new funding for milk banks](#), June 2018; [Hearts Milk Bank website](#); [NorthWest Milk Bank website](#); [Human Milk Bank Association of North America](#); [Australian government website](#); [Anales de Pediatria, Recommendations for the creation and operation of maternal milk banks in Spain, 2018](#); [Human Milk Foundation](#)
6. Chu S, Procaskey A, Tripp S, Naples M, White H, Rhein L. *Quality improvement initiative to decrease time to full feeds and central line utilization among infants born less than or equal to 32 0/7 weeks through compliance with standardized feeding guidelines*. J Perinatol 2019;39(8):1140-1148.
7. (a) Perrin MT. *Donor human milk and fortifier use in United States level 2, 3 and 4 neonatal care hospitals*. J Pediatr Gastroenterol Nutr 2018 Apr;66(4):664-669. (b) Thoene MK, et al. *Improving nutrition outcomes for infants < 1500 grams with a progressive, evidenced-based enteral feeding protocol*. Nutr Clin Pract 2018;33:647-655[1].
8. Buckle A, Taylor C. *Cost and cost-effectiveness of donor human milk to prevent necrotizing enterocolitis: systematic review*. Breastfeed Med 2017;12:528-536.
9. Mahon J, Claxton L, Wood H. *Modelling the cost-effectiveness of human milk and breastfeeding in preterm infants in the United Kingdom*. Health Econ Rev 2016;6:54 [doi:10.1186/s13561-016-0136-0].
10. Taylor C, Joolay Y, Buckle A, Lilford R. *Prioritising allocation of donor human breast milk amongst very low birthweight infants in middle-income countries*. Matern Child Nutr 2018;14 Suppl 6:e12595.