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Use of Donor Human Milk and Maternal Breastfeeding Rates: a Systematic Review

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Review

Abstract

The number of human milk banks is growing worldwide. The introduction of donor human milk (DHM) to neonatal units has been advocated as a strategy to promote maternal breastfeeding. However, concern has been raised that the introduction of DHM may actually lead to a decrease in maternal breastfeeding. To address this question, we conducted a systematic literature review of studies that assessed maternal breastfeeding rates before and after the introduction of DHM. We searched 7 electronic databases, carried out citation tracking, and contacted experts in the field. Where data for breastfeeding rates before and after the introduction of DHM were directly comparable, a relative risk was calculated. Our search identified **286** studies, of which **10** met the inclusion criteria. Definitions of patient populations and study outcomes varied, limiting meaningful comparison. Where possible, relative risks (RR) were calculated on aggregated data. The introduction of DHM had **a significant positive impact** on any breastfeeding on discharge (RR 1.19, 1.06-1.35, $p=0.005$), but none on exclusive maternal breastfeeding on discharge (RR 1.12, 0.91- 1.40, $p= 0.27$) or on exclusive administration of own mother's milk (OMM) days 1-28 of life (RR 1.08, 0.78-1.49, $p 0.65$). A single centre study demonstrated a significant decrease in the percentage of feeds which were OMM after the introduction of DHM. In conclusion, the available data demonstrate **some evidence of positive and negative** effects on measures of maternal breastfeeding when DHM is introduced to a neonatal unit.

Introduction

Donor human milk (DHM) is used in neonatal intensive care units (NICUs) for the feeding of preterm infants when own mother's milk (OMM) is not available or insufficient. A recent Cochrane review ¹ showed that in preterm and low birth weight infants, feeding with formula compared with DHM results in a higher risk of developing necrotizing enterocolitis (NEC). As the incidence of NEC increases in relation to the other complications of preterm birth ² there is growing interest worldwide in the use of DHM.

Currently, it is estimated that there are about 500 human milk banks (HMBs) in existence in over 37 countries. ³ In addition, the number of HMBs is known to be growing in countries with large populations like India, ⁴ and the first HMB in Russia was recently established in Moscow. ⁵ DHM is currently recommended by the World Health Organization (WHO), ⁶ the American Academy of Pediatrics (AAP), ⁷ and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), ⁸ as the preferred alternative to OMM if this is not available for low birth weight (WHO) or preterm (AAP, ESPGHAN) infants. In the United States, the proportion of NICUs using DHM increased from 25% in 2007 to 45% in 2011. ⁹

Despite this, there remain many neonatal units that do not use DHM, for a variety of reasons including cost, uncertainty about the evidence base for its use, and parental preferences. ¹⁰ A 2014 survey of level 3 and 4 NICUs in the United States ¹⁰ showed that that 41% of respondents did not use DHM for their patients. Similarly, a survey of special care baby units, local neonatal units and NICUs in the United Kingdom, ¹¹ also carried out in 2014, showed that 39% of respondents did not initiate infants on DHM.

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5 If the use of DHM continues to increase, a key question is how that this may impact on
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7 maternal breastfeeding rates. A national survey in Italy showed that neonatal units associated
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9 with a HMB have higher rates of maternal breastfeeding on discharge.¹² Using this data,
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11 these authors argued that the introduction of DHM may serve to extend a culture of
12
13 breastfeeding. **Similarly, others have argued that DHM should be considered a**
14
15 **supportive measure to mothers expressing milk for their preterm infants, and have used**
16
17 **it as part of package of measures to try to increase maternal breastfeeding rates¹³ and**
18
19 **promote a culture of using only human milk¹⁴ on NICUs.** However, **anecdotally,**
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21 concerns have been raised that the introduction of DHM to a NICU may in fact discourage
22
23 maternal breastfeeding.^{13,14} **In addition, the authors of one study have shown that**
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25 **promoting DHM can lead to an unintended decrease in the use of OMM, perhaps by**
26
27 **providing an "acceptable alternative" to the initiation and maintenance of lactation.¹⁵**
28
29 **There is thus uncertainty as to whether the further introduction of DHM will impact**
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31 **either positively or negatively on maternal breastfeeding rates in NICUs.**
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39 Two large trials in North America are currently addressing the question of whether there are
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41 clinical benefits to infants of using DHM compared to formula.^{16,17} However, because these
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43 trials are both blinded, impacts on health professional or maternal behaviors will not be fully
44
45 determined. Thus, the aim of this review was to strengthen the evidence base for the use of
46
47 DHM, and to determine the effects of DHM provision on measures of OMM use during
48
49 admission and on breastfeeding rates at discharge. We addressed the following research
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51 question: in mothers with an infant admitted to a neonatal unit (Population), what are the
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53 effects of using DHM (Intervention) versus formula milk (Comparison) on maternal
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55 breastfeeding rates in, and on discharge from, the NICU (Outcome). Given the complexity of
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3 DHM as an intervention, we anticipated there might be relatively few randomized controlled
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5 trials (RCTs), and that cluster trials and/or observational studies would require research
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7 synthesis.
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10 11 **Methods**

12 13 *Searches*

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18 This review and the manuscript reporting it was prepared according to the PRISMA
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20 guidelines,¹⁸ and the completed PRISMA checklist is available in Supplementary Appendix
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22 S1. We carried out a systematic literature review in October 2014 using the following
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24 databases: Medline,¹⁹ Embase²⁰ and Global Health²¹ (all using the OVID interface),²² The
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26 Cochrane Library,²³ CINAHL,²⁴ Global Health Library,²⁵ and Current Controlled Trials.²⁶
27
28 Search terms were generated using MESH and Emtree terms relating to breast milk, infant
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30 formula, milk banks, milk donation and neonatal units, with input from a medical librarian. A
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32 complete list of search terms, formatted for each database, is available within the study
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34 protocol in Supplementary Appendix S2. The review is registered on PROSPERO,²⁷
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36 CRD42014013162.
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43 Databases were searched from 1946 onwards. Only papers with abstracts published in the
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45 Latin alphabet were reviewed, and these were translated if necessary by one of the authors
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47 (TW). We conducted reference searches of the studies which met the inclusion criteria,
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49 carried out citation tracking of these studies via Google Scholar,²⁸ and contacted experts in
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51 the field in North America, Europe and Australia to identify further relevant studies. Two
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53 reviewers (TW and JS) independently assessed the papers identified in the screening search
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55 using the inclusion and exclusion criteria.
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Inclusion/exclusion criteria

Studies were included if 1) the study was original research, 2) the study was a controlled trial with participants allocated randomly, or an observational trial examining the impact on maternal OMM provision or breastfeeding rates pre and post introduction of DHM to a neonatal unit, 3) the study population was infants admitted to a neonatal unit, 4) the study specifically compared enteral feeding with DHM versus formula and 5) the study provided quantitative data on maternal breastfeeding rates during the admission or on discharge.

Studies were excluded if the patient population included infants in postnatal or pediatric wards, or did not compare donor breast milk directly with formula. Study types that were excluded were 1) case reports or opinion pieces without primary data or 2) qualitative studies that did not provide data on the proportion of mothers breastfeeding during the admission or on discharge.

Data extraction, assessment of study quality and risk of bias

The following data were extracted from the studies meeting the inclusion criteria: authors, study setting and country where it took place, research question/study aims, definition of patient population, outcome measure, study sample size, rates of breast milk use prior to introduction of donor milk to a unit, and rates of breast milk use after the introduction of donor milk. Where data was given for breastfeeding rates on discharge, it was noted where this was on discharge from, and the definition of the time period used (eg within 48 hours of discharge). Data were entered onto Microsoft Excel.

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3 In order to assess the risk of bias within each individual study, we applied principles from the
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5 Cochrane Collaboration and the Working Group for Grading of Recommendations
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7 Assessment, Development and Evaluation.²⁹ Modifying a scoring system used previously by
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9 one of us,³⁰ we assessed the quality of each study as being high, moderate, or low, according
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11 to study design, sample size, quality of the control group, calculation of an odds ratio/relative
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13 risk, confounding factors, and the geographical spread of studies. Details of the scoring
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15 system can be found in Supplementary Appendix S3.
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20 In order to assess the risk of bias across studies, we noted whether or not each study had been
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22 published in a peer reviewed journal. We contacted the principle authors of each included
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24 study to ascertain if they could share any unpublished data that might influence the
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26 cumulative evidence available. Finally, we contacted experts in the field to ensure there were
27
28 no large datasets that were unavailable due to publication bias.
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32 33 34 ***Data analysis*** 35

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38 Where data for breastfeeding rates after the introduction of DHM were directly comparable
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40 between studies, the numbers of infants in each group were aggregated and a relative risk
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42 with a 95% confidence interval was calculated.³¹ The exposure for these calculations was the
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44 introduction of DHM to a neonatal unit. Where data was not comparable between studies, the
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46 outcomes pre and post the introduction of DHM were extracted, and it was noted whether a
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48 summary measure had been calculated.
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52 53 54 **Results**

55 56 ***Searches*** 57 58 59 60

Our database search yielded 374 records, and consultation with experts in the field identified **4** further studies. Citation tracking of studies that met the inclusion criteria yielded 25 additional records, and after excluding duplicates a total of **286** studies were screened. **Fourteen** of these studies were selected for full text review, of which **10** studies met the inclusion criteria (Figure 1). Of the remaining 4, 1 was excluded as it duplicated data from an included study,³² 1 was not based in a neonatal unit,³³ 1 did not compare breastfeeding rates before and after the introduction of DHM,³⁴ and 1 provided no quantitative data on breastfeeding rates.³⁵ **Six** of the included studies were based in the United States^{13,14,36-38}, **2** in Spain^{39,40} and 1 study in the United Kingdom,⁴¹ and Australia⁴² respectively. All the studies were published since 2008, but included data on infants born between 2001 and 2014. Table 1 provides a summary of the study characteristics.

Quality assessment and risk of bias

The assessment of study quality is shown in Table 2. **One of the studies was judged to be of high quality,**³⁹ **7** of the studies were assessed to be of moderate quality,^{14,36-38,41} and the remaining 2^{13,42} to be of low quality. Only 1 study was prospective and interventional,¹⁴ and only **2** included more than one hospital site.¹³ Two studies included DHM as part of a bundle of measures designed to increase maternal breastfeeding rates^{13,14}. **Six** were published in peer reviewed journals,^{13,14,36,37,40} and **4** were conference abstracts.^{38,41,42} None of the contacted authors of the included studies shared unpublished data to contribute to our analysis. Consultation with experts in the field did not reveal any large unpublished data series relevant to this review.

Definitions

There was substantial heterogeneity in the definition of the patient population in the included studies. One study looked at infants born at < 30 weeks gestation,⁴² 2 studies examined infants born at < 32 weeks gestation or with a birth weight (BW) of <1.5kg,^{13,40} 5 studies used a BW <1.5kg as the inclusion criteria,^{36–38,41,43} 1 study used BW < 2 kg¹⁴ and 1 study used BW < 1kg.³⁹ Outcome definitions were similarly heterogeneous and were comparable in 4 studies for any breastfeeding on discharge,^{14,39,40,43} and in 2 studies for exclusive breastfeeding on discharge,^{40,42} and exclusive administration of OMM days 1-28.^{37,40} Only one study⁴⁰ defined a time period before discharge for the receipt of breast milk (48 hours), and none of the studies defined how that breast milk was given on discharge. **Five studies did not document whether all infants or only surviving infants were used as the denominator for measures of maternal breastfeeding;**^{13,14,36,38,42,43} **3 excluded infants who died from their analysis,**^{37,40,41} **and 1 study included these in the denominator.**³⁹ **When performing calculations the denominators used were those given by the authors and no adjustments were made for the infants who died, as these numbers were small.**

Studies also varied in how DHM had been introduced to a neonatal unit. Three studies looked at changes in the administration of OMM after the introduction of a milk bank to a neonatal unit.^{40–42} Two studies examined whether there was a change in practice after the introduction of DHM as part of a bundle aimed to increase the use of human milk.^{13,14} One examined changes in practice after a new policy specifying use of DHM when not enough OMM was available³⁷ and the remaining 4 examined changes in practice after the introduction of DHM to a neonatal unit.^{36,38,39,43}

Effects of introduction of DHM on maternal breastfeeding rates

Two studies^{40,42} examined the effect of the introduction of DHM on exclusive maternal breastfeeding rates on discharge. One of these provided no definition of “exclusive breastfeeding” on discharge, and the studies included two different patient population groups (born at < 30 weeks⁴² vs born at <32 weeks or BW <1.5 kg).⁴⁰ Aggregating the data showed no significant difference between the two groups, with a relative risk of 1.12 (CI 0.91- 1.40, $p= 0.27$) of breastfeeding on discharge after the introduction of DHM.

Four studies^{14,39,40,43} provided data on infants receiving any breastfeeding on discharge after the introduction of DHM. In one of these studies¹⁴ DHM was introduced as part of a program aimed to increase the volume of human milk given to infants born at less than 2 kg. No significant difference ($p=0.09$) was found in infants receiving any breast feeds on discharge after the introduction of the program. No formal definition was given of “any breastfeeding on discharge” in this study. **Another study**⁴³ **found a significant increase ($p=0.02$) in any breast feeding on discharge after the introduction of DHM milk to a neonatal unit**. Patient population groups differed between the 4 study groups (BW< 2 kg,¹⁴ <1.5kg,⁴³ < 1 kg³⁹ and born at <32 weeks or BW <1.5 kg).⁴⁰ Aggregating the data for the **4 studies, a significant difference was found between the two groups (relative risk: 1.19; CI 1.06-1.35, $p=0.005$), showing an increase in maternal breastfeeding after the introduction of DHM.**

Two studies^{37,40} examined the effect of the introduction of DHM on the exclusive administration of OMM in the first 28 days of life. One used a patient population of infants born at <32 weeks³⁷ and another looked at infants born at <32 weeks or with a BW < 1.5 kg.

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⁴⁰ In the second study, there was a reduction (from 40% to 13%) in the percentage of infants receiving exclusive OMM. According to the authors, this was because after the introduction of DHM, it was used when there was not enough milk from the infants' own mothers, whereas prior to the introduction of DHM, infants were fed by parenteral nutrition the first days of their lives to avoid infant formula. Aggregating the data, no significant difference was found between the two groups (RR 1.08; CI 0.78-1.49, $p=0.65$). All the data above is shown in Supplementary Appendix S4.

Single studies provided data on a number of variables related to the use of OMM after the introduction of DHM (Table 1). A single center study judged to be of moderate quality found that the introduction of DHM was associated with a significant decrease in the percentage of feeds which were OMM days 1-14 ($p<0.01$) and days 1-28 ($p=0.04$) of life.³⁸ One study examined the % of exclusive OMM given until full feeds were established⁴¹ and found no significant difference ($p=0.51$) between the pre and post DHM groups. One study examined the % of feeds that contained >50% OMM given to infants of up to 34 weeks corrected gestational age,³⁶ and again found no difference between the groups ($p=0.95$). Two studies looked at the % of OMM given (as volume) for days 1-14¹³ and 1-28 of life³⁷ respectively but did not calculate a statistical summary measure.

Discussion

Interest in the use of DHM has increased over the last decade, manifest by a worldwide expansion in the number of HMBs. Despite this there remains a relative lack of high quality research into the impact of DHM on the recipient neonatal population or its wider societal effects. Our systematic review of the use of DHM on maternal breastfeeding rates confirmed

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3 this lack of high quality data, identifying only **10** studies that met the inclusion criteria. These
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5 studies were geographically limited, available from only 4 countries, and the majority of the
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7 included studies (**6/10**) were from the United States. **Four** of the **10** included studies were
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9 conference abstracts and were therefore not peer reviewed. Using a scoring system to assess
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11 study quality, **only 1 was** judged to be of high quality.
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16 The available data demonstrates **mixed effects** on measures of maternal breastfeeding when
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18 DHM is introduced to a neonatal unit. **Relative risk calculations with aggregated data**
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20 **from 4 studies did show a significant increase in any breastfeeding on discharge after**
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22 **the introduction of DHM. However, there appeared to be no effect on exclusive**
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24 **breastfeeding on discharge or the exclusive administration of OMM in the first 28 days**
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26 **of life after the introduction of DHM.** Even where DHM was introduced as part of a care
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28 bundle (as it was in 2 of the included studies),^{13,14} in individual centers there appeared to be
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30 no significant increase in measures of maternal breastfeeding. Conversely, 1 of the **10** studies
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32 showed a statistically significant decrease in the use of OMM after the introduction of DHM.
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36 ³⁸ **This was posited by the authors to be due to the fact that the provision of DHM was**
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38 **discouraging mother from expressing breastmilk.** However, the remainder of the available
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40 evidence does not support the hypothesis that the introduction of DHM has an adverse effect
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42 upon breastfeeding rates in NICUs.
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47 **Some of the heterogeneity in results may reflect the fact that DHM can be used in a**
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49 **variety of ways. One study described DHM as a “bridge” to be used until a mother is**
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51 **able to express enough milk for her preterm infant,¹³ whereas others describe the**
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53 **rationale for DHM as being a way to reduce the volume of formula feeds being given to**
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55 **preterm infants¹⁴ or as a means to more rapidly introduce enteral feeds.⁴⁰ Given that**
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3 **DHM is introduced for a variety of reasons, and in a variety of ways (as part of package**
4 **of measures, by opening a HMB, or by replacing preterm formula in feeding**
5 **guidelines), it is perhaps not surprising that no consistent effect is seen on measures of**
6 **maternal breastfeeding.**
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11 12 13 14 *Limitations*

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18 Inclusion criteria and definitions of outcomes varied between the studies, precluding a
19 formalized assessment of a risk of bias using a funnel plot. Where aggregated relative risks
20 were calculated, study groups patient populations differed in terms of birth weight and
21 gestation, **and whether they included infants who had died in their denominator,**
22 **although the number of these was small.** Our data samples were small for each variable,
23 and the calculated intervals were wide, so that small but important effects in either direction
24 **could not be excluded for exclusive breast feeding on discharge or use of OMM in the**
25 **first 28 days of life. For other outcomes, the heterogeneity of study variables and patient**
26 **populations limited the ability to meta-analyse the data. We are unable to comment on**
27 **whether having consistent definitions of patient population and study outcomes would**
28 **have supported a positive effect of DHM on other indicators of maternal breast feeding**
29 **success. However, it is likely that the larger data sets permitted by consistent definitions**
30 **would have allowed a more definitive answer to the question of whether DHM impacts**
31 **on these.**
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51 **Eight** out of the **10** studies were retrospective, and there was a high risk of bias, with **only 1**
52 **study** judged to be of high quality. We attempted to rule out publication bias by contacting
53 experts in the field to see whether substantial unpublished databases existed on this topic, and
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3 could not find evidence for any. However, it remains possible that reports of trials with
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5 negative findings have not entered peer reviewed journals or been accepted for conferences.
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7 In addition, we were unable to obtain unpublished data from the included studies on
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9 breastfeeding rates that may have influenced our results.
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14 Whilst we chose to concentrate on surrogate markers of how much OMM was provided
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16 during admission and on discharge, the introduction of DHM to a neonatal unit may impact
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18 on other important outcomes. These include rates of OMM initiation, the duration of
19
20 provision of OMM, the total proportion of human milk (ie OMM and DHM) given to infants
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22 during their admission, the length of hospital admission, and practices related to the
23
24 fortification of human milk. Thus the narrow focus of our research question may limit the
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26 applicability of the findings of this systematic review.
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34 **Conclusion**

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38 **In summary, the available data demonstrate positive effects on some, but not all,**
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40 **measures of maternal breastfeeding rates when DHM is introduced to a neonatal unit.**
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42 **There is also some evidence that in certain settings rates might actually decrease.**
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44 **However, overall there is probably sufficient data available to re-assure clinicians that**
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46 **the introduction of DHM in itself is unlikely to adversely affect breastfeeding rates. If**
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48 **the introduction of DHM is to be promoted as a cost effective way of promoting**
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50 **maternal breastfeeding, further well designed studies with standardized populations,**
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52 **consistent use of DHM, measurable breastfeeding outcomes and economic evaluation**
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54 **may help to inform uniformity of practice.** Ideally these could be integrated into large
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3 randomized controlled trials looking at the effects of DHM on clinical variables such as
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5 mortality, NEC, sepsis and longer term health benefits.
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9 **Funding Source:** Funding for travel allowing the participants to meet to plan this research
10 was provided by the British Association of Perinatal Medicine (BAPM).
11

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32 **Figure 1.** PRISMA Flow Chart

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34 **Table 1.** Summary of Study Characteristics.

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36 **Table 2.** Quality Assessment

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39 **Supplementary Appendix S1.** PRISMA Checklist

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43 **Supplementary Appendix S2.** Review protocol

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46 **Supplementary Appendix S3.** Quality Assessment Methodology

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49 **Supplementary Appendix S4.** Calculation of Relative Risk

Figure 1: PRISMA Flow Diagram

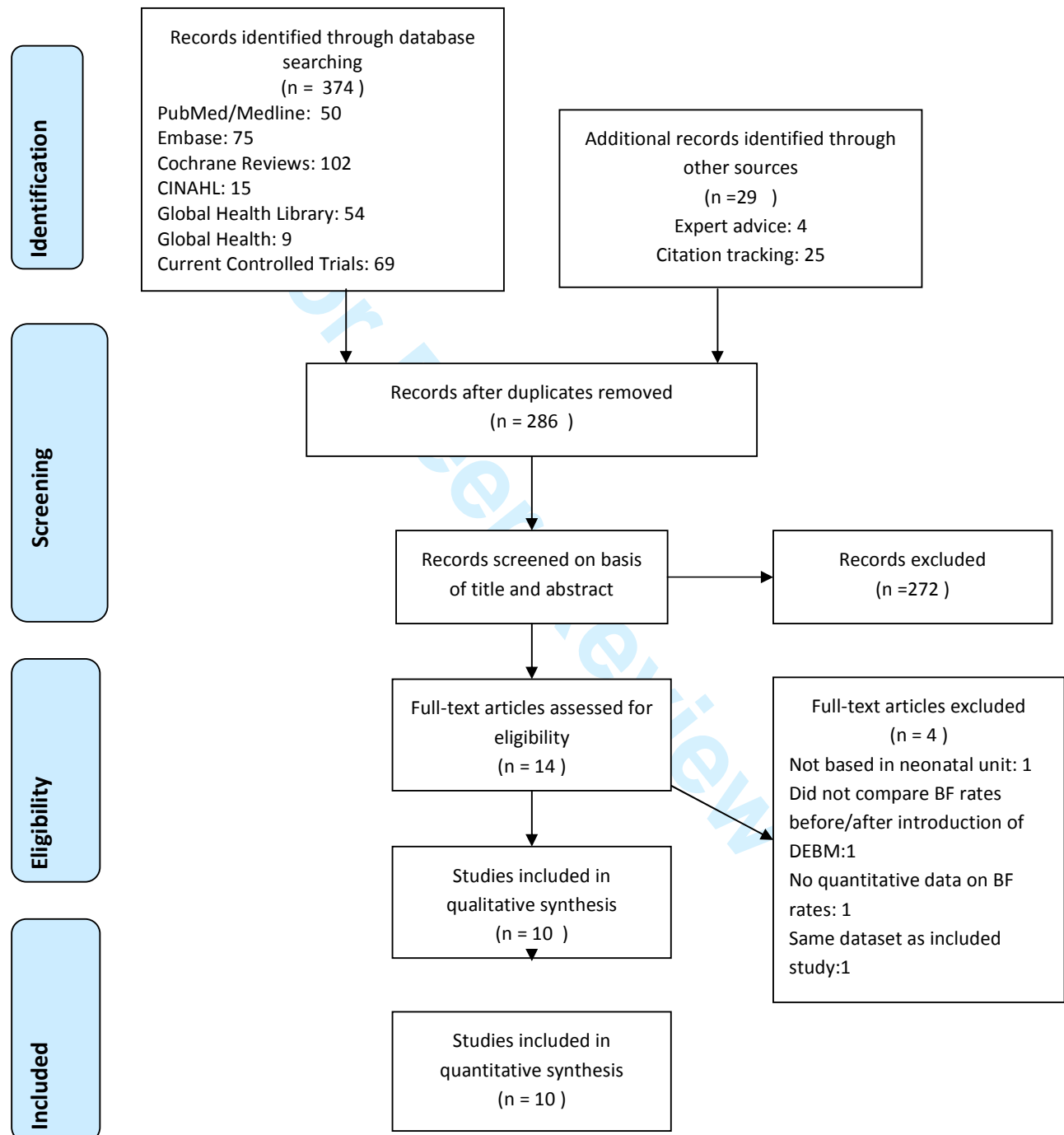


Table 1: Summary of Study Characteristics

Authors	Study setting (country)	Research Question/ Study Aims	Definition of patient population	Outcome	Study sample size	Main findings
Beasmore <i>et al</i>	NICU (United Kingdom)	Did the introduction of a HMB change OMM and formula milk usage during the establishment of enteral feeding.	BW <1.5 kg	% exclusive OMM until full enteral feeds achieved	122	65% pre vs 70% post, p= 0.51
Bishop <i>et al</i>	NICU (United States)	To assess the influence of DHM on the incidence of NEC and the amount of OMM use.	BW <1.5 kg	% of feeds that contained >50% OMM up to 34 weeks CGA	331	51% pre vs 54% post, p=0.95
Delfosse <i>et al</i>	Level 4 NICU (United States)	To determine acceptance of DHM for feeding preterm infants and whether offering DHM alters OMM feeding.	Born at < 32 weeks or BW <1.5 kg	% OMM given (volume) days 1-14 of life	650	63% at start of intervention vs 60% at end of intervention, no p value calculated
Esquerra-Zwiers <i>et al</i>	Level 4 NICU (United States)	To evaluate the impact of a DHM program on OMM and formula feedings.	BW <1.5 kg	% feeds which were OMM days 1-14 of life.	265	85% pre vs 68% post, p= < 0.01
				% feeds which were OMM days 1-28 of life.	265	71% pre vs 61% post, p= 0.04
Kok <i>et al</i>	Neonatal Unit (Australia)	The effects of the introduction of a HMB on the feeding of preterm infants on discharge.	Born at < 30 weeks	Exclusive BF on discharge from neonatal unit (not specified further)	155	53% pre vs 64% post, no p value calculated

1 2 3 4 5 6 7 8	Marinelli <i>et al</i>	Level 4 NICU (United States)	To compare enteral intake type in preterm infants before versus after establishing a DHM policy.	BW<1.5 kg	% OMM given (volume) days 1-28	154	66% pre vs 70% post, no p value calculated
9 10 11 12					Exclusive administration of OMM days 1-28	154	38 % pre vs 55% post, no p value calculated
13 14 15 16 17	Montgomery <i>et al</i>	Level 3 NICU (United States)	To assess the effects of a program designed to improve human milk availability for preterm infants on breast milk use and feeding-related outcomes.	BW <2 kg	Receiving any BF on discharge home (not specified further)	245	44% pre vs 53% post, p=0.09
18 19 20 21 22 23 24	Parker <i>et al</i>	Level 3 NICU (United States)	To determine whether rates of consumption of OMM at discharge home changed in the 2 years pre and post implementation of a DHM program.	BW <1.5 kg	Any BF on discharge from hospital (not specified further)	154	43% pre vs. 65% post, p=0.02
25 26 27 28 29 30	Torres <i>et al</i>	Neonatal Unit (Spain)	To assess the impact that opening a HMB had on the proportion of infants breastfeeding at discharge and other practices related to feeding.	Born at <32 weeks or BW <1.5 kg	Exclusive BF on discharge from hospital (within 48 hours of discharge)	104	54% pre vs 56% post, p=0.87
31 32 33 34 35 36					Any BF on discharge from hospital (within 48 hours of discharge)	104	86% pre vs 78% post, p=0.27
37 38 39 40 41					Exclusive administration of OMM days 1-28	104	40 % pre vs 13% post, no p value calculated

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Verd et al	NICUs (Spain)	To assess the impact of an exclusive human milk diet to nourish extremely low birth weight infants in the neonatal intensive care unit	BW <1.5 kg	Any BF on discharge from hospital (not specified further)	201	67% pre vs 70% post, p=0.74
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Abbreviations: NICU: Neonatal Intensive Care Unit; DHM: Donor Human Milk; OMM: Own Mother’s Milk; HMB: Human Milk Bank; BW: Birth Weight; CGA: Corrected Gestational Age; BF: Breastfeeding.

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Table 2: Quality Assessment

Authors	Study design (score)	Sample size (score)	Quality of control group (score)	Calculation of OR/RR (score)	Confounding factors (score)	Geographical spread (score)	Score (quality of study)
Beasmore <i>et al</i>	Retrospective observational (0)	122 (1)	Demographic variables noted, no differences (2)	Yes (2)	None (2)	Data from 1 unit (0)	7 (moderate)
Bishop <i>et al</i>	Retrospective observational (0)	331 (1)	Demographic variables noted, no differences (2)	Yes (2)	None (2)	Data from 1 unit (0)	7 (moderate)
Delfosse <i>et al</i>	Retrospective observational (0)	650 (2)	No control group (0)	No (0)	DHM introduced as part of bundle (1)	Data from 2 units (1)	4 (low)
Esquerra-Zwiers <i>et al</i>	Retrospective observational (0)	265 (1)	Demographic variables noted, no differences (2)	Yes (2)	No data (0)	Data from 1 unit (0)	5 (moderate)
Kok <i>et al</i>	Retrospective observational (0)	155 (1)	No demographic variables documented (0)	No (0)	No data (0)	Data from 1 unit (0)	1 (low)
Marinelli <i>et al</i>	Prospective cohort study (1)	154 (1)	Demographic variables noted, significant differences (1)	Yes (2)	None (2)	Data from 1 unit (0)	7 (moderate)
Montgomery <i>et al</i>	Prospective interventional (2)	245 (1)	Demographic variables noted, significant differences (1)	Yes (2)	DHM introduced as part of bundle (1)	Data from 1 unit (0)	7 (moderate)
Parker <i>et al</i>	Retrospective observational (0)	154 (1)	Demographic variables noted, no comment on whether significant differences between	Yes (2)	None (2)	Data from 1 unit (0)	5 (moderate)

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groups (0)							
<i>Torres et al</i>	Retrospective observational (0)	122 (1)	Demographic variables documented, significant differences (1)	Yes(2)	None (2)	Data from 1 unit (0)	6 (moderate)
<i>Verd et al</i>	Retrospective observational (0)	201 (1)	Demographic variables documented, no differences (2)	Yes (2)	None (2)	Data from 4 units (2)	9 (high)

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