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Meeting Report

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Abbreviations

Table 1 List of Abbreviations

Abbreviation	Definition
AIBLUD	Italian Association of Human Milk Banks
BF	Breastfeeding
BFHI	Baby Friendly Hospital Initiative
BMS	Breastmilk Substitutes
DHM	Donor Human Milk
EMBA	European Milk Bank Association
HIC	High-income Country
HMB	Human Milk Bank
HMBANA	Human Milk Bank Association of North America
HTST	High-Temperature-Short-Time Processing
LBW	Low birth weight
LMIC	Low- and Middle-income Country
MOM	Mother's Own Milk
MPHO	Medical Product of Human Origin
NEC	Necrotising Enterocolitis
NICU	Neonatal Intensive Care Unit
PDHM	Pasteurised Donor Human Milk
RCT	Randomised controlled trial
SDGs	Sustainable Development Goals
SME	Subject Matter Expert
UNICEF	United Nations International Children's Emergency Fund
VLBW	Very low birth weight
WHO	World Health Organization

- **The authors agree that language should be as inclusive as possible when discussing infant feeding. Please note that for brevity and consistency the use of the terms breastfeeding, breastmilk, mother's own milk and mother have been used throughout this document. This is not intended to detract from alternative terminology that readers may prefer to use.**
- **The references cited throughout the document are those that had been published at the time of the meeting. Where useful papers and other documents have been published**

subsequently these are listed separately at the end of the references section in the Addendum (page 86).

Executive Summary

Breastfeeding is recognised as an essential part of newborn care. Human milk offers optimal infant nutrition and health due to its balanced composition of both macro and micronutrients and an abundance of anti-infective, protective and health promoting constituents that cannot be provided by alternative newborn and infant foods. Where a mother's own milk is not available or is insufficient, DHM processed by an HMB is a safe alternative. Currently, HMBs exist in over 65 countries with the vast majority situated in North America, Brazil, and Europe. Rapidly increasing numbers have been established in India and China over the past decade, and a small but growing number now operate in low and middle-income countries where the health and economic burden of preterm, low birthweight infants are the highest. Most WHO member states have yet to establish national policies or programmes that support the provision of DHM to infants who need it. The ability to provide human milk to all infants who need it has the added benefit of contributing to a country's ability to achieve other health and development commitments relating to human rights, sustainable development goals (SDGs) and targets for maternal, infant and young child nutrition.

In July 2019, a group of international experts in fields relevant to human milk banking gathered at a meeting organised by the Institute of Biomedical Ethics, University of Zurich, and co-sponsored by the World Health Organization. This meeting was prompted by the growing interest globally in creating and sustaining human milk banks, and addressing current safety and ethical concerns and standards. The need for authoritative global guidance on human milk banking as a necessary next step has been highlighted in calls for action. The term 'human milk bank' was used to mean a facility where DHM is collected, screened, processed, stored and subsequently distributed to meet the needs of infants admitted to a healthcare centre.

The aims of this meeting were to define knowledge gaps with regard to human milk banking, determine the need for global guidelines and the frame of such guidelines, and provide recommendations on steps that need to be taken at the international level. Participants were chosen to ensure both regional and professional representation. Three previously commissioned background documents helped develop a common understanding of the currently operational human milk banking systems, recognize their known gaps, and compare the management of milk banks with that of blood,

tissue and cell banks. The background documents included a scoping paper and a literature review on the technical aspects of human milk banking, an update on its global status and a review of national tissue banking programmes and their cross-applicability to human milk banking.

The report outlines the introductory and background information presented, the key findings and a summary of the discussion from the expert consultation that followed the presentations which were shared by the WHO attendees and the co-authors of the background documents. Whole group targeted discussions identified knowledge gaps and challenges including how donor human milk should be classified, its importance as a source of nutrition and immunological support, and its cost effectiveness. The lack of current data, the ethical considerations that require further exploration, the integration of human milk banks into health systems, and the use of donor human milk in optimal lactation support were also discussed.

A further exploration of the discussion points raised took place in working groups with the underlying theme being the need to legitimize donor human milk through the publication of WHO standards. Specific areas identified for discussion in the three groups were Integration into Systems, Strategy and Policy, and Quality and Safety. Each group was tasked with discussing the issues, the challenges, the research gaps, the potential minimum standards, and the potential global guidance or tools needed pertaining to the group topics. The groups were asked to pay special attention to the ethical issues relevant to the topic of discussion.

The work of these groups was presented and used to develop the conclusions from the meeting and the recommendations for how best to proceed, which included those related to maternal lactation such as:

- early and frequent expression (within 1 hour of delivery and 8 times or more in 24 hours)
- skin to skin contact
- ensuring optimal volume production by 14 days
- that sick and vulnerable infants have access to MOM during at least the first 28 days of life
- monitoring exclusive and any breastfeeding for a defined period (e.g., 6 months post hospital stay).

A SWOT analysis evaluating DHM was devised for use by governments and departments of health in their evaluation of DHM. Strengths included the physiological and clinical benefits of DHM (e.g., reduction in NEC), the benefits for donors, and consistency with SDGs 1,2,3,5 & 10. Some of the

weaknesses were identified as the need for readiness for milk bank infrastructures, a lack of lactation specialists and of comparative data on DHM, unclear indications for its use, and the possibility of cultural and religious barriers. The opportunities included advocacy for vulnerable infants, the strengthening of breastfeeding and the availability of MOM, the Early Child Development agenda, improvements in human milk donation, the facilitation of international collaboration and research, the generation of standards, discussions around ethics, and improvements in holistic newborn care. The threats listed included the costs and the sustainability of milk banks, donor recruitment and their potential exploitation, resistance from healthcare workers, safety and quality issues, conflicts with commercial interests, and the lack of lactation and breastfeeding support for mothers and the consequent overuse of DHM.

There was a clear consensus throughout the discussions that all infants should have equitable access to optimal nutrition, and that facilitating breastfeeding and the availability of MOM as the preferred and optimal nutrition source should be fully supported, wherever possible. Furthermore, the terminology used in discussing optimal nutrition systems for infants should be clearly defined to differentiate between direct breastfeeding, MOM, PDHM and other milks. DHM is the next best alternative but due to limited research, the composition of optimal DHM and its necessary properties is difficult to define. This results in variations in its composition with regard to its nutrient and non-nutrient properties, and these will have clinical implications. Whilst PDHM should be prioritised for use in VLBW infants in the absence of MOM, even in the absence of currently published research, there is potential for the use of PDHM in other vulnerable populations, to facilitate an exclusively human milk diet and to avoid supplementation with formula.

A series of minimum standards for HMBs was agreed as part of the discussions. These included that the focus should be on the different needs of all vulnerable and sick infants, not just preterm infants; and that HMBs should be organized within a healthcare system, rather than be freestanding within a community; that regulation and quality assurance measures should be in place as should context-dependent considerations of ethical issues and high quality, evidence-based lactation care, together with a number of human milk metrics to gauge this, including the establishment of values of how many mothers of term and preterm infants should achieve early breastfeeding / milk expression and how many sick and vulnerable infants should receive MOM for the first 28 days. Finally, as a minimum standard, HMBs should observe the legal considerations of their state and country.

An array of knowledge gaps impeding the formulation of best practices with regard to the banking of DHM were identified, including the cost-effectiveness of the use of PDHM in LMIC settings, the lack of evidence regarding optimal processes such as pasteurisation and fortification techniques where relevant, the lack of medical evidence as to which specific populations may benefit from DHM (apart from neonates at risk of necrotising enterocolitis or feeding intolerance), and difficulties in measuring outcomes. There is also no evidence at present for the use of PDHM on preventing NEC outside the NICU setting, e.g., in a paediatric cardiology ward. Various practical challenges with the establishment of HMBs in a range of settings were also identified. These included the inappropriate use of DHM and the possible exploitation of human milk providers in profit-driven human milk processing operations. The need for the availability of training opportunities and competency assessment was also identified to help avoid the misuse of DHM and to ensure safe practices within milk banking operations.

Given the expansion of and interest in human milk banking, particularly in LMICs, the overall conclusion was that evidence-based guidance is urgently needed. No trans-global guidance exists on the implementation, operation and regulation of HMBs. Furthermore, no further support has been established at a global level for ensuring the safe use of DHM for infants in need. Closing the research gaps will be an important next step driving the process of developing context-driven recommendations, minimum standards and guidance tools for the donation, use, storage and distribution of human milk.

Meeting Introduction

In July 2019, a group of international experts in fields relevant to human milk banking gathered at a meeting organised by the Institute of Biomedical Ethics, University of Zurich, and co-sponsored by the World Health Organization (WHO).

This meeting was prompted by the growing interest globally in creating and sustaining human milk banks (HMBs), and addressing current safety and ethical concerns and standards. The need for authoritative global guidance on human milk banking as a necessary next step has been highlighted in calls for action (DeMarchis et al., 2017).

Human milk is essential for optimal infant nutrition and health due to its balanced composition of both macro and micronutrients and an abundance of anti-infective, protective and health promoting constituents that cannot be provided by alternative newborn and infant foods (Rollins et al., 2016). WHO and UNICEF prioritise donor human milk (DHM) as the recommended alternative for low birthweight infants when a mother's own milk (MOM) is unavailable or insufficient, in settings where HMBs are available or can be established (WHO, 2011). In practice, this would include most settings dealing with neonates. Despite these recommendations, and notwithstanding the publication of national and international guidelines, recommendations and minimum standards (Borja et al., 2013; Calvo et al., 2018; Cederholm et al.; Child Health Division Ministry of Health and Family Welfare Government of India, 2017; Hartmann et al., 2007; Human Milk Banking Association of North America (HMBANA), 2018; Italian Association of Human Milk Banks (AIBLUD) & Ministry of Health Working Group, 2014; Weaver et al., 2019), no transglobal guidelines exists on the implementation, operation and regulation of HMBs. Furthermore, no further support has been established at a global level for ensuring the safe use of DHM for infants in need.

Aim and Scope of the Meeting

The aims of this meeting were to:

1. Define knowledge gaps with regard to human milk banking
2. Determine the need for global guidelines with regard to human milk banking
3. Determine the framework of such guidelines, if deemed necessary, and
4. Provide recommendations on steps that need to be taken at the international level.

The term ‘human milk bank’ as discussed in this meeting is a facility where DHM is collected, screened, processed, stored and subsequently distributed to meet the needs of infants admitted to a healthcare centre (to be distinguished from peer-to-peer milk sharing networks, or milk banks used for other purposes such as the provision of DHM to non-hospitalised infants, and as a more general support for lactation and breastfeeding of infants in the community).

The choice of participants for the meeting ensured both multi-cultural experience and regional representations based on the WHO grouping of member states with representation in the following regions: Africa, Americas, South and Southeast Asia, Europe, Eastern Mediterranean, and Western Pacific, and professional representation of various stakeholder and expert groups relating to human milk banking. Expert representation involved the following fields:

- Nutritional sciences
- Food safety and regulation authorities
- Health law
- Biomedical ethics
- Healthcare professionals relating to women’s and children’s health:
    - Lactation consultants
    - Midwives
    - Neonatologists
    - Perinatal nurses
    - Paediatricians
    - Clinical Dietitians
- Managers / technical directors of human milk banks
- Clinical researchers with a special interest in lactation and human milk
- Public health:
    - Nutrition
    - Child development
    - Infectious diseases:
        - Focus on medical products of human origin (MPHOs)
- Microbiology
- Pharmacology:
    - Drug excretion into milk
- Blood safety
- Tissue banking

- Patient-donor organisation representatives

Taking into consideration the varied levels of understanding among participants outside their area of expertise, three background documents were commissioned to help develop a common understanding of the currently operational human milk banking systems, recognise their known gaps, and compare the management of milk banks with that of other tissue and cell banks. The background documents by the subject matter experts (SMEs) were commissioned as follows:

1. A scoping paper and literature review on the technical aspects of human milk banking and donor human milk:

   An outline of what is known in the available scientific literature in relation to the technical aspects of human milk banking, as well as gaps in technical knowledge.

2. The global status of human milk banking:

   An overview of the current practices in human milk banking worldwide, including general figures and national policies, regulatory frameworks, operational models, needs in various resource settings, and barriers and supportive elements in establishing human milk banks.

3. A review of national tissue banking programmes (with a view to cross-applicability to human milk banking):

   A multi-disciplinary review to apply insights from established national tissue-banking programmes to the identification and establishment of the main components necessary for a first framework of a national human milk banking programme.

The documents were made available to participants prior to the meeting proper and were shared as presentations by the SME authors at the onset of the meeting, to facilitate dialogue and allow for any necessary clarifications. These documents, which are fully referenced, are available on request.

In the presentation of the background papers, participants were asked to keep in mind:

i. Content that should clearly be considered for inclusion in guidance
ii. Content that should clearly not be subject to regulation (for example, because it would harm HMBs with low-volume throughput, or because the content was irrelevant)

iii. Knowledge gaps, especially with regard to the practical challenges of milk banking and contested issues.

These presentations were followed by a discussion with the aim of defining the scope and purpose of the global guidance required, as well as further actions.

We present here the introductory and background information provided, the key findings from the background documents and the discussion from the expert consultation that followed.

Background

This section is based on the opening presentation provided by Dr Laurence M. Grummer-Strawn and Mr Efstratios Chatzixiros, and follows its structure.

Introduction

Breastfeeding is recognised as an essential part of newborn care (Rollins et al., 2016). Where MOM is not available or insufficient, DHM processed by an HMB is a safe alternative (WHO, 2011). Currently, HMBs exist in over 65 countries with the vast majority situated in North America, Brazil, and Europe. Rapidly increasing numbers have been established in India and China over the past decade and a small but growing number now operate in low and middle-income countries where the health and economic burden of preterm, low birthweight infants are the highest (PATH, 2013). Most WHO member states have yet to establish national policies or programmes that support the provision of DHM to infants who need it. The ability to provide human milk to all infants who need it has the added benefit of contributing to a country's ability to achieve other health and development commitments relating to human rights, SDGs, and targets for maternal, infant and young child nutrition.

DHM as a Medical Product of Human Origin

DHM is considered a 'medical product of human origin' (MPHO) by the WHO (WHO, 2017). An MPHO refers to biological material, derived wholly or in part from the human body and processed using human labour and technological intervention, and intended for clinical application. For many diseases with no other available treatment, the use of MPHOs can be a vital intervention to prolong life, reduce morbidity and improve the quality of life. MPHOs fall into the category of 'universal coverage', in that

everyone should have access to life-saving products. A distinct set of principles applies when it comes to the donation and management of MPHOs (WHO, 2017). Among these are concerns for the dignity and human rights of donors, particularly their own rights to health and the security of their own person; mitigating the risks to public health through appropriate donor selection, screening, and testing; processing the MPHO to prevent disease transmission and to ensure traceability in the event of a sentinel event; and to level inequalities in access to MPHOs.

New MPHO Principles

Many of the ten principles (WHO, 2017) for promoting ethical practices in the donation and management of MPHOs, can be applicable to DHM:

Principle 1

"Governments are responsible for ensuring the ethical and effective procurement, distribution and use of medical products of human origin. This responsibility includes the obligation to develop and enforce regulations to ensure the maximum possible level of safety, quality and efficacy, both within and across national borders."

Most WHO member states have yet to establish binding national policies or programmes that support the provision of DHM to infants who would benefit from it. In the few WHO member states which have established national policies, DHM is not consistently classified as an MPHO, and is therefore regulated by different legal frameworks or not at all. Other classifications of DHM include classification as a food substance, a nutritional therapy or in a new category of its own. The WHO is now engaged in the development of product-specific material based upon the Common Framework on MPHOs, with human milk identified as one such product. Human milk would benefit from the quality and safety details and ethical considerations that have been laid out for other MPHOs.

Other principles of the Common Framework on MPHOs relevant to DHM are as follows:

Principle 3

"Outside clinical research and for the advancement of science, medical products of human origin should be used only in situations of clinical utility and in the absence of alternative and affordable therapies with a comparable or more favourable balance of risks and benefits."

The optimal use of DHM supports the maintenance of an exclusive human milk diet while the mother's lactation is becoming fully established and able to eventually meet her infant's full nutrient needs (Adhisivam et al., 2019; Williams et al., 2016). Whilst breastmilk substitutes (BMS) are available, these do not offer a more favourable balance of risks and benefits, given their implication in the pathogenesis of necrotising enterocolitis (NEC), and higher rates of sepsis (compared with maternal milk) in preterm infants, and their potential to induce inflammation of gut endothelium and disrupt optimal gut microbiota. DHM is preferable to infant formula when used as a bridge to, and not a substitute for, MOM, although the potential nutritional deficiencies associated with the use of heat processed DHM with preterm infants may need to be considered, especially if DHM is used for a longer period. Concerns remain about the availability of DHM and support for milk banks potentially siphoning support from assisting mothers with establishing and maintaining their own milk production. Additionally, on a busy neonatal unit, the ready availability of DHM potentially offers a more convenient and less time-consuming activity than the provision of optimal support for lactation and the establishment of breastfeeding. Rarely, a mother may want to feed her baby human milk but not intend to breastfeed herself, wishing to rely instead on DHM. Guidance on the optimal use of DHM would prevent its potential overuse and suboptimal use or misuse.

For the purposes of this meeting, the scope was mainly limited to human milk banking services established to provide DHM for premature and vulnerable infants. At the same time, it was recognised that DHM may be beneficial for other infants (Arnold, 1990; Reimers et al., 2018) and in clinical use cases beyond infant health. For example, the use of modified human alpha-lactalbumin (a protein found in human milk) is currently undergoing clinical trials for its therapeutic properties against bladder cancer.

Principle 5

"Policies governing compensation to persons who provide biological materials for use as medical products of human origin should seek to guard against the exploitation of vulnerable individuals and promote equity in donation. The best way to achieve these goals is to adhere to a policy of financial neutrality, in which persons who donate their biological materials for use as medical products of human origin should neither benefit nor lose financially as a result of the donation. Countries should ensure that the burden of donating these materials does not fall primarily on economically disadvantaged groups."

Principle 6

"Prospective and actual donors of human biological materials for use in medical products should be protected against physical and psychosocial risks to the fullest extent possible."

This follows from the principle of seeking to guard against the exploitation of vulnerable individuals, protecting both mother (donor and the recipient's mother) and infant (donor's and the recipient), and promoting equity in donation. Donors whose baseline health and nutritional status may already be poor may risk maternal depletion in the process of lactogenesis, which requires an incremental increase in nutrients consumed, their mobilisation from maternal stores and a greater energy consumption. There is also the potential to cause harm to their own babies if their milk is diverted from their babies towards provision to others by selling their milk to benefit from incentives. (AFP, 2017).

Financial compensation for donating breastmilk has been a long-debated issue, due to the potential positive and negative consequences. The provision of incentives for providing human milk may encourage the coercion and exploitation of women from poor financial backgrounds, with women from low-income families making most donations to support themselves and their families. It may stigmatise donors, disincentivising other women who wish to contribute to HMBs. Financial incentives may also compel women to conceal personal practices and aspects of their medical history that may jeopardise their provision of human milk, and hence their pay-out. While certain medications and pathogens can be tested for, it is important to ensure as safe a supply as possible coming into the system to protect the recipients of DHM.

Principle 7

"Depending on the product, and in addition to other information routinely provided when offering medical products of human origin to prospective recipients, the human origin of the product should be disclosed without compromising the confidentiality of the donor's identity."

The concept of anonymity poses an issue depending on the context and the cultural significance of the donation. The extent to which directed donations take place outside of an HMB, where a lactating woman provides (freely or for a fee) human milk to a specific infant is largely unknown. Some women may want to develop a relationship with the recipient family. For example, accounts have shown it to

be helpful for mothers who have lost their own infants to see the impact of their donated milk on another mother-child dyad as part of their grieving process (Douglas, 2009).

The use of DHM may raise religious concerns for some families, particularly those of Muslim faith, due to the concept of 'milk-kinship'. Specifically, according to this principle, kinship develops between the offspring of the milk donor and the recipient of the DHM, and restricts marriage between the two. Consulting with the country's Islamic religious councils and asking permission or fatwa from the religious leaders has enabled the establishment of milk banks in some countries (e.g., Iran and Singapore). In many settings, it is culturally important to also work with religious leaders on messaging and communications and to ensure the appropriateness of the model from the ground up. Meetings may be arranged between the donor and recipient parents before the milk exchange takes place in countries where it is required for the identities of both children to be disclosed (Kuwait, Indonesia). Records may also be maintained for a longer duration compared to non-Muslim settings. However, anonymity may also be accepted due to the absence of suckling, the potential for negative health impacts resulting from the absence of human milk and the milk transforming processes involved in the milk banking operations (Ghaly, 2012).

Principle 8

"Equity in access to the benefits of medical products of human origin should be promoted by sustained efforts to remove barriers to access. Any waiting lists and allocation systems that are developed for medical products of human origin should be based on clinical criteria and ethical norms, not considerations of financial or social status."

In the UK, as well as in other countries in Europe, DHM is provided free of charge to recipient families by the healthcare providers. In other systems, insurance or healthcare providers may not cover the provision of DHM, and families have to pay for it. Hence, allocation systems may preferentially favour infants of higher socio-economic status, leading to inequity in terms of benefiting from the donation of human milk.

There are many local guidelines, and hospitals often set both donation and recipient criteria. National and international guidelines also exist and provide more widely available recommendations (Borja et al., 2013; Calvo et al., 2018; Cederholm et al., 2016; Child Health Division Ministry of Health and Family Welfare Government of India, 2017; Hartmann et al., 2007; Human Milk Banking Association of North America (HMBANA), 2018; Italian Association of Human Milk Banks (AIBLUD) & Ministry of Health

Working Group, 2014; National Institute for Health and Care Excellence (NICE), 2010; Weaver et al., 2019). However, there are no clear global guidelines ensuring equity in terms of how milk should be collected or distributed. Some governments have policies on the buying, selling and exporting of DHM, developed in response to commercial activities, and these have served to curtail such activities (AFP, 2017).

Principle 9

"In order to minimise the risk of harm to donors and recipients and to protect the stability and sustainability of services for medical products of human origin, all steps in the development and use of medical products of human origin should be fully traceable and subject to effective quality-management systems and vigilance and surveillance programmes."

In common with the banking of other MPHOs, traceability is a particular concern and challenge in milk banking. Specifically, DHM in some programmes may be pooled from one mother or pooled together from several different donors, and feeds happen regularly over a potentially long period of time (several months, occasionally longer). Human milk banking services are often managed separately from the location of the clinical use of the DHM, making traceability from donor mother to recipient infant potentially challenging.

New WHO Strategic Priorities

Breastfeeding is critical for achieving global goals on nutrition, health and survival, economic growth, and environmental sustainability. The Baby Friendly Hospital Initiative (BFHI) is a global effort to implement practices that protect, promote and support breastfeeding. According to the BFHI, any facility with preterm infants and other vulnerable newborns should feed them with human milk. Where MOM is unavailable or insufficient, especially for low birthweight, very low birth weight, and otherwise vulnerable infants, they should be fed DHM (WHO & UNICEF, 2018). Supplies of DHM need to be established and provided in a safe manner. Supporting breastfeeding and the provision of DHM in the absence of MOM, can be seen in the context of the strategic priorities of the WHO's 'Triple Billion Target'. This target aims to ensure one billion more people benefit from universal health coverage, one billion more people are better protected from health emergencies, and one billion more people enjoy better health and well-being.

Policies and standards for quality and safety, and guidance on the establishment, operation and regulation of HMBs have been proposed, and member countries have indicated interest in prioritising guidance for human milk banking and for the WHO to take further action.

Key Points from Presentations

The co-authors presented an overview of each of the three background documents that had been made available to the meeting attendees prior to the meeting. These key points are described in the following sections.

Technical Considerations on Human Milk Banking

Deborah O'Connor & Sharon Unger

Donor human milk is defined as human milk, in excess of an infant's current and future needs, that is donated by a lactating mother for use by a recipient infant that is not the mother's own infant. A human milk bank refers to a service established to recruit human milk donors, collect donated milk, and then screen, process, store and distribute the milk to meet infants' specific needs for optimal health. Some HMBs are part of a hospital facility or a related human milk feeding enterprise, while many are separate entities (PATH, 2019b).

Variability in Milk Composition

Human milk is a complex fluid that changes according to many maternal and infant variables, and batches of DHM can vary widely in their composition. For example, fat, which makes up 50% of the energy in human milk, can vary from 2.0 to 6.0 g/dl in milk received in a hospital enteral feeding preparation room (de Halleux & Rigo, 2013). The most significant variable impacting the composition of milk is the lactational stage, although even the composition of mature milk changes over time. There are several models of HMB processes employed to ensure the blending of nutrients and a reduction in milk variability. Some milk banking models that operate in low- and middle-income countries rely on milk donation from mothers of neonatal intensive care unit (NICU) babies who are present in the hospital or from those who are practicing kangaroo mother care on the postnatal wards. The milk from these mothers may be very early milk, including colostrum and transitional milk, as they often donate all the milk that their infant does not consume because of a lack of storage facilities.

Other factors that may influence milk composition include maternal factors (most importantly, genetics, diet, supplements and body mass index), and methods of milk collection (e.g., fore milk vs. hind milk, drip milk, and completeness of breast expression). To address the variability in nutrients, some milk banking associations or local guidelines recommend donated milk be pooled from multiple mothers (e.g., 3-5 donors (Human Milk Banking Association of North America (HMBANA)). Care is taken in the field of human milk and lactation to not inadvertently raise concerns among women about the nutrient-variability of their milk, as worries regarding the quality of their milk have been cited as reasons for discontinuing human milk feeding.

Screening and Selection of Human Milk Donors

The screening of donors as part of the selection process is designed to minimise the risk to infants of the transfer of pathogens, such as viruses and other harmful microorganisms, into the milk that is donated. While the natural microbiome found in MOM is beneficial in colonising their own infant's gastrointestinal tract, these same organisms may be pathogenic when DHM is fed to vulnerable infants. For some preterm, low birthweight or sick infants, even commensal organisms may be harmful. Reducing the transmission of pathogens that may harm an infant starts with donor selection. It is beneficial that potential donor screening is performed by well trained staff with appropriate professional qualifications such as nurses, midwives, medical doctors, nutritionists, dietitians and lactation consultants. The choice of staff may differ according to the region.

While variability among milk banks exists between geographical locations, this is mainly due to economic factors rather than fundamental differences in the assessment of risk. In North America and Europe, the initial screening interview is designed to establish:

i. That the potential donor has or is likely to produce a minimum volume of milk (this is in consideration of logistics costs)
ii. That the donor and infant are in good health (exceptions exist in the case of bereaved donors and those whose infants remain under clinical care within hospital or post discharge and their future nutritional and non-nutritional requirements have been considered)
iii. Donor lifestyle and behaviours relevant to the safety of the donation.

This is followed by the following procedures:

i. Informed consent for intended use of DHM
ii. Serology – using the established standards required for Medical Products of Human Origin (MPHOs) such as blood, tissues, cells and organs (e.g., HIV-1, HIV-2, HTLV-1, HTLV-2, Hepatitis B and C, syphilis), with the addition of nucleic acid testing at some banks. Testing at the time of recruitment is a usual standard; however past serology test results are accepted in some low- and middle-income settings.
iii. Obtaining approval from the donor's physician and the infant's paediatrician to proceed with the donation (North America).

Donor exclusions at HMBs typically follow the same policies as for the local blood services. The exclusion criteria in the United States are set by the HMBANA guidelines (Human Milk Banking Association of North America (HMBANA), 2018). The European Milk Bank Association has published recommendations (Weaver et al., 2019) which mirror those included in the Guide to the Quality and Safety of Tissues and Cells for human application published by the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe (European Directorate for the Quality of Medicines & HealthCare (EDQM), 2019). However, milk banks in Europe follow country-specific guidelines as well as local regulatory considerations and requirements.

Guidance is provided in person, or given over the phone and/or to new donors with video instruction, on how to express milk to reduce the bacterial load, and to explain the logistics of safely handling, storing and transporting the expressed milk to the bank. Transportation of frozen milk from the home or hospital to the HMB is largely arranged by the bank using recognised and trained couriers.

Testing of human milk, including acceptance criteria, varies between and within countries and regions. Culture of a representative milk sample is the standard in most regions; however throughout much of Europe, guidelines mainly recommend the culturing of milk both prior to and after pasteurisation. This is not a requirement of the HMBANA guideline where a post-pasteurisation culture alone is the standard (additional tests may be carried out in accordance with local protocols). In some European countries, human milk that meets stricter acceptance criteria may be fed raw without undergoing heat treatment (Grøvslien & Grønn, 2009; Kühn, 2017).

Other significant facility quality control measures are typically in place to ensure the safety of DHM. These include for example: sufficient staff training, protocols for equipment and maintenance, record-keeping, and audits both with regard to food safety and as a donation facility.

Processing of DHM

Fresh DHM usually goes through two freeze-thaw cycles and multiple container changes to produce pasteurised ready-to-feed DHM. In some low resource settings milk may be pasteurised without having been frozen and without a container change. The most usual scenario includes the container the milk is collected in during the act of milk expression being frozen prior to donation, remaining frozen during transportation to the milk bank, being thawed prior to transfer to a large vessel for pooling (single or multiple donor pooling), aliquoting of the milk into containers for the pasteurisation process and subsequent freezing whilst test results are awaited. Once the post pasteurisation milk

culture is seen to be negative, the frozen DHM is issued to the recipient hospital ward or unit where it remains frozen until needed. It is then thawed and transferred to a syringe or a smaller container prior to feeding, or thawed in a central milk kitchen, aliquoted and delivered as a feed-sized volume to the recipient.

Freezing and thawing affects both nutrients and bioactive substances. For example, freezing affects the physical properties of fat globules in milk, resulting in increased adherence to feeding containers and reducing the energy content of the milk during container changes. Most milk banks process raw milk using Holder pasteurisation, in which milk is held at 62.5°C for 30 minutes. In practice, depending on the rates of heating and cooling, DHM may be warmed for an hour or longer. While there is good retention of most nutrients and some bioactive substances, there are also substances that are drastically reduced or eliminated, with live cells being the most affected (Ewaschuk et al., 2011).
The effect of Holder pasteurisation on bile salt-dependent lipase is of particular concern. Most of the fat contained in human milk is present as triglycerides. Fatty acids need to be removed from the glycerol backbone to be absorbed. The stark reduction of bile salt-dependent lipase post-Holder pasteurisation is hypothesised to further diminish the fat and energy content available to infants via DHM.

There is an on-going effort to develop alternative methods of processing DHM. The European Milk Bank Association (EMBA) provides recommendations on how to evaluate such technology.
High-temperature-short-time processing (HTST), currently used in processing milk from the dairy industry, is one such alternative. If the high-temperature period is short enough, it may be able to better preserve bioactive components including the retention of some bile salt-stimulated lipase (BSSL) activity. However, its feasibility has been questioned as it may not be sufficient to destroy all pathogens, for example non-lipid-enveloped viruses (Peila et al., 2017). Newly designed HTST pasteurisers have recently been specifically designed and validated for human milk processing (Escuder-Vieco et al., 2018; Moro et al., 2019).

Two non-thermal methods are also being explored with the aim of increasing the retention of bioactive components. These are high hydrostatic pressure processing, and ultraviolet-C radiation (Pitino et al., 2019). Although promising, there are limitations such as the availability of equipment and the ability of milk banks to accommodate bulky equipment, that currently present as barriers to their use. Using different methods may expand what we know now in terms of post-processing DHM composition, requiring flexibility in thinking about the composition of human milk.

Effect of DHM on Infant Health Parameters

A Cochrane review published in 2018 (Quigley et al., 2018), and since updated (see Addendum), evaluated the evidence comparing formula milk and DHM for feeding preterm or low birth weight infants, when the mother's milk was not available. Many studies were dated, having been performed more than 30 years ago, and infant characteristics (e.g., improved survival at earlier gestational ages), and clinical practices have changed since then, including nutrient fortification of human milk. Gains in weight, head circumference and length all favoured the use of formula milk in comparison with DHM. The review was clear, however, that the use of supplemental DHM did prevent NEC. There were no differences seen in long-term growth or neurodevelopment. Further, meta-analysis of two available studies showed feeding intolerance was improved with DHM. An improved feeding tolerance meant that infants could be weaned from parenteral nutrition and be fed enterally instead.

A further Cochrane review in 2016 (Brown et al., 2016), and since updated (see Addendum), evaluated multi-nutrient fortification of human milk on preterm infants. The authors identified 14 (18) trials in which 1071 (1456) preterm infants were included. Meta-analysis of the studies showed short-term increases in weight, linear gains and head circumference growth with nutrient fortification of human milk. Importantly, no adverse effects were noted with the multi-nutrient fortifier use, including NEC, even though most fortifiers are bovine based. As there was an absence of data on the longer-term growth and developmental effects, the authors concluded that additional trials are needed to resolve this issue.

A randomised clinical trial (O'Connor et al., 2016), comparing the effect of supplemental multi-nutrient fortified DHM with preterm formula in very low birth weight infants, showed an overall decline in weight and length-for-age z-scores in both groups of infants at the end of the feeding intervention, although there was no statistically significant difference between the groups. This suggests that it is feasible to fortify DHM to produce growth similar to that of infants who are fed preterm formula, but future research is required on how to best support the growth of both groups of very low birth weight infants.

Fortification of DHM

Human milk does not contain an adequate supply of several nutrients including protein, calcium and phosphorus required to meet the elevated needs of the very low birth weight infant (i.e., <1500 g)

and support growth. Fortification of human milk is used extensively in tertiary care NICUs worldwide, mainly in high income countries. Several types of commercially produced multi-nutrient fortifiers that have been designed for preterm infants are available for purchase. In addition to protein, other macronutrients, vitamins and minerals are typical components of fortifier formulations. In low resource settings, an alternative strategy is often used to enrich human milk by adding cow's milk formula powder to achieve the required level of nutrient enrichment.

Long-Term and Post-Discharge Use of DHM

DHM is mainly used to supplement inadequate supplies of MOM for preterm, low birthweight and sick hospitalised infants. Its use forms a bridge enabling exclusive human milk feeds whilst the infant's mother establishes her own milk supply and ultimately exclusive breastfeeding or breastmilk feeding. Less frequently, in the absence of any MOM, DHM provides all of the infant's enteral feeds, and this may persist for several weeks or occasionally months in infants at high risk of developing NEC or where alternatives are not available. The use of DHM post-discharge from neonatal units and for full-term infants in the community is limited although more frequent in some settings such as Brazil. Which infants in any given jurisdiction are provided with DHM as a supplement will depend on DHM availability, funding mechanisms, clinician knowledge of the evidence in support of its use and their experience with DHM. In most settings, DHM is prioritised for the most vulnerable infants and most specifically preterm infants at risk of NEC. Infants are at risk of NEC until about 34 weeks post-conception (Yee et al., 2012).

It is uncertain whether DHM, as processed today with its freeze/thaw cycles, multiple container changes and heat treatment, is a complete source of nutrition on its own. The nutrient composition of DHM post-processing differs from that of fresh MOM. In addition to suboptimal protein, calcium and phosphorus levels for preterm and very low birthweight infants, pasteurised DHM (PDHM) may not meet the requirements of term and appropriately grown infants for heat-sensitive nutrients without micronutrient supplementation. Folate, for example, is an essential nutrient required for cell division and growth, and it is especially important in the neonatal period when early rapid growth occurs. An adequate intake of folate for a healthy term-born infant is estimated to be 65 micrograms (mcg) per day (Food and Nutrition Board et al., 2011), and the average folate content of human milk is estimated to be 85 mcg/l. Assuming a neonate has an intake of 780 ml/day of DHM, after freezer-storage at -20°C for three months (up to 50% reduction of folate) and Holder pasteurisation (up to 25% reduction of folate) (Pitino et al., 2019), 26.5 mcg of folate per day would be provided to an infant. It is questionable whether this is enough to meet the nutrition requirements of a healthy term-born

infant fed exclusively on DHM for six months and exemplifies the importance of evidence in determining best practices. If DHM is given to healthy term infants, a suitable multivitamin should be considered. In addition to nutrient losses, the loss of enzyme activity and the reduction of some hormones affects nutrient availability and utilisation.

Motivations for Donating Human Milk

The literature elucidating motivations behind donating human milk is limited. Potential motivations for donating human milk include feelings of altruism and comfort knowing their human milk produced is going to a good use, and encouragement from healthcare professionals to donate their milk. The opportunity for some bereaved mothers to donate their milk is also reported to aid the grieving process. These motivations remain under-researched.

The increasing commercialisation of human milk, whereby its provision is financially rewarded, has raised questions around the impact of payments on availability, safety and ethical acceptability. In some countries, federal law prohibits payment for biological materials including human milk. This is the case in Canada, for example.

Ethical Issues Related to Human Milk Banking

Although member milk banks of HMBANA do not pay mothers for the donation of human milk, there are for-profit companies operating in the United States that do, with human milk treated as a commodity. It is important for informed consent to be obtained from both donors, who should understand how their donation is being used, and recipients of human milk. Clinicians and policymakers need to remain vigilant for both conflicts of interest with for-profit companies that may affect decision-making about the use of DHM, and for research that has been funded by such companies (see Ethical Considerations for additional discussion of ethical issues).

Authors' Conclusions

MOM is acknowledged to be the optimal way to feed infants. MOM needs to be distinguished from PDHM with an understanding of how the latter has been processed. At the local level, especially in busy neonatal units, PDHM may be used more than it should be, with best practice being PDHM as a bridge to MOM. Like MOM, supplemental DHM reduces the risk of NEC and improves feeding tolerance but, unlike MOM, it may not improve long-term neurodevelopment. With future developments in processing capability, the composition of DHM and its corresponding uses and outcomes may improve.

Points of Discussion for Technical Considerations on Human Milk Banking

1. Improving the Composition of DHM

The way DHM is collected and processed may make the nutrient and bioactive composition of the final product differ from MOM more than necessary. The closer DHM resembles MOM, the closer the benefits of DHM may come to MOM. It is not just the thermal processes (i.e., pasteurisation) that have an impact on the constituents of DHM. Pre-pasteurisation processes such as the collection of milk at later stages of lactation, freezing/thawing and container changes all impact the composition of milk. For example, freezer storage is associated with a decrease in the bioactive substances found in milk, such as lactoferrin, a known antimicrobial. The reduction of important bioactive substances in DHM could explain the lack of beneficial impact of DHM on sepsis compared to MOM, among other things. Caution should be taken in analysing DHM as structural changes in DHM may impact the analysis. For example, processing DHM causes lactoferrin to aggregate. When lactoferrin is measured using standard laboratory methodology, it appears to be lower than the true amount that might be available to the infant after digestion and disaggregation in the stomach.

Maximising the quality without compromising the safety of the milk should be a priority for research into human milk banking. Fully understanding the practical and economic factors involved in the decision-making process is also key to improving the nutritional and immunological quality of DHM.

In some settings, using unpasteurised milk might be the solution to retaining optimal composition. In Norway, DHM is mainly used without pasteurisation and in Germany, some HMBs provide raw milk in addition to pasteurised. The availability of raw DHM allows its composition to resemble MOM more closely. If guidelines are developed as globally acceptable standards for DHM, it will be necessary to take into consideration these different practices.

It is useful to consider how DHM is used before determining the necessary technical requirements and the ideal composition of DHM post-processing. A small number of babies may never receive any maternal milk, due to possible maternal morbidity or mortality. Most babies receive DHM for a short time before, or as a supplement to, receiving MOM, as it may take longer for the mother's milk to come in when she is ill or has delivered at a preterm gestation. It is unclear if the composition of DHM really needs to be optimised to resemble MOM, when an infant is likely to receive very small amounts

of DHM for a short period. While caution should be taken with infants fed exclusively on DHM, the concept of requiring very small amounts of DHM for a short period of time should be the norm. Optimal and appropriate support should be given to all parents who are able to express milk so that infants can transition as soon as possible to exclusively MOM.

2. Screening

It would be beneficial to have a global unified list of travel restrictions, medications and non-medicinal substances that would result in the deferral of DHM donations. Such lists take a lot of time and expertise to create and continuously update. At present, these restrictions differ between and sometimes within countries, as a result of inconsistent recommendations. Emerging viruses present questions requiring timely answers which may not yet be immediately available locally.

3. Evaluating Outcomes – Measuring Infant Growth

Growth is commonly used as a proxy for assessing the nutritional adequacy of feeds provided to vulnerable hospitalised infants. For preterm infants, the goal has been to try to achieve intra-uterine accretion rates of weight gain of 15g/kg/day. Available evidence suggests that to maximise neuro-development, the rate of weight gain should be at least 18g/kg/day (Ehrenkranz et al., 2006).

A variety of growth charts are available to assess the growth of infants. It is recommended that the WHO growth standards and the INTERGROWTH 21st charts be used to assess the postnatal growth of term-born and preterm infants (Villar et al., 2015). The latter charts begin at 27 weeks post-conceptional age and hence are not useful for the least mature infants in tertiary care.
Fenton charts (Fenton & Kim, 2013) were used for research studies on premature babies who did not fall on the INTERGROWTH 21st charts, which are now being modified to include the Fenton chart. These modified growth charts could be used in future studies.

Global Overview and Status of Human Milk Banking

Kiersten Israel-Ballard, Kimberly Mansen & Cyril Engmann

Human Milk Banking Overview

In the absence of any official coordinating global body, data collection and the ability to accurately assess and convey the precise global milk banking situation including milk banks' exact locations, operations and activity is challenging. Together with inputs from human milk banking teams around the world, PATH has created a map indicating milk banking locations using their own data where supplied (not all HMBs responded to requests for information), and estimates that there are more than 600 milk banks in 60 countries. Most of these are in high resource settings – North America, Europe and South America, with over 220 milk banks in Brazil alone (*Human Milk Bank Global Map*). Milk banks are much fewer in number in low resourced regions of the world including the Middle East, Africa, South Asia and Southeast Asia, although their numbers are increasing.

A Technical Advisory Group Meeting on human milk banking was convened by PATH in 2012. The meeting aimed to identify the activities and core principles that should drive milk banks. Although milk banks have different resources, the consensus was that they should all adhere to components of safety, quality, networking and information-sharing, awareness, advocacy and promotion, and sustainability. Most milk banks only adopt some of these principles. The output of this meeting was the first Global Implementation Framework (version 1.0) outlining these core principles for integrating human milk banking and ensuring quality and safety (PATH, 2013).

Current infant indicators do not show how vulnerable infants around the world are being fed or what kind of support is given to their mothers. PATH has observed that up to 40% of babies in NICUs around the world may not have access to their mother's milk in the first hours or days of life (Israel-Ballard, 2018), and perhaps even longer. Whilst some of these may benefit from the availability of DHM, mothers, who might themselves be in critical care settings, may not be getting the additional support they require in order to provide their own milk to their babies. These issues are systems level issues and may not relate to DHM.

Barriers to Effective Scale-Up

In current practice, DHM is primarily to be used for a short period of time, usually relating to a mother being ill, having had a C-section or a difficult labour, or a premature delivery with delayed lactogenesis. Long-term use of DHM might relate to the mothers' inability to breastfeed, medications preventing her from breastfeeding, or breast surgery, but there is a lack of data around the long-term use of DHM.

Infants may also be orphaned or abandoned, precluding them from MOM. The rates of orphaned and abandoned infants differ around the world. Data around the true need for DHM and the number of infants requiring at least one feed is not well understood due to a lack of routine data collection on early feeding, especially for this population. Outside the infant nutrition setting, DHM is also being used in cancer care, both as an adjunct to treatment and as a nutritional supplement. The appropriateness of this and other special use cases should be further discussed.

Regarding infant nutrition, the WHO guidance is that DHM should function as a replacement for formula use, but not as a replacement for MOM. Ideally DHM should be used as a bridge while initiating and transitioning to full MOM. Ascertaining the most appropriate clinical indications for the use of DHM, and whether these should form part of milk banking guidelines, remain unanswered questions.

There are a few main reasons preventing milk banks from being scaled up to meet demand. These include:

1. A lack of data. There is an absence of comprehensive data on how babies are being fed in NICU settings world-wide. If available, this would better inform how many babies would benefit from DHM. The current global indicators with routine tracking systems use recall data, which may be inaccurate especially among mothers who were sick themselves, or who had a preterm baby. Rigorous, multi-country studies are needed to understand how infants are fed in the first days of life.
2. A need for innovations to improve the quality of the final product, facilitate safety procedures and reduce costs.
3. A lack of reliable information, in the absence of a global reference with regard to setting up a milk bank, especially in countries where such expertise does not exist.
4. A failure to integrate milk banks into broader maternal and newborn care, thus limiting their effectiveness.
5. A historical policy misalignment between the interests of nutrition (which promotes breastfeeding and the issues associated with DHM) and the priorities of newborn care

which, in the millennium development goals era, focused on the term infant who died or was sick outside of facility-based settings, usually from readily preventable health problems.

Higher income countries have the resources to adopt systems from other high-income settings and to utilize equipment and supplies designed for the high resource context. Alternatively, some high to middle-income countries also seek to evaluate and adapt milk banking to their individual settings – revising policies based on experience and trying new technologies to improve processes and costs. However, many lower-resource settings around the world are new to milk banking and do not have resources for infrastructure, procurement or staffing with this experience. They may also not have expertise from other fields readily available as part of their health systems, for example that related to microbial testing and screening milk. This poses a challenge to the implementation of milk banks in lower-resource settings, where processes have to be created or adapted to be functionable.

Human Milk Bank Processes

The processes involved in human milk banking generally include selective donor recruitment and screening, sanitary milk expression, temperature-controlled milk handling, pasteurisation, bacteriological testing, temperature-controlled transport and finally, milk allocation to infants. When well-developed, the entire process has safety standards embedded at each step. These safety standards are often specific to the setting in which the HMB has been developed and may not be declared explicitly. Countries looking to set up a new milk bank by selectively picking and choosing processes from various available guidelines risk compromising elements of safety.

The inconsistency between HMBs in how terminology is defined further complicates these issues. This leads to a lack of clarity in milk banking practices and further affects the ability to compare systems. For example, the term ‘pooling of milk’ could refer to either the pooling of DHM from a single donor mother, or the pooling of milk among multiple donors, depending on the milk bank in question.

Before initiating a milk bank, it is important to recognise the culture surrounding human milk in the particular setting. This includes the culture of human milk in terms of the relationship between mother and infant, as a product, and as part of a larger system. Government oversight is often needed to implement milk banking as part of the health system, and to provide support and guidance on a national level, especially to ensure sustainability.

Many milk banks have little control over how DHM is eventually used. In practice, the end-distribution of DHM tends to be the domain of clinical staff, although hospital administration staff may determine whether it is used at all through their purchasing decisions. When conceptualising guidance, it is important to consider both the collection and interaction with the donor and the recipient of the DHM, and to consider when and how those two disparate, but closely related systems meet. It is also important to distinguish guidance for milk banks that are already in operation from guidance for new milk banks, because some of the recommendations for a well-functioning HMB within an adequate system may be different from those related to an HMB being newly established.

Operational Models of HMBs

Milk banks have been operationalised in various ways. Most existing milk banks are run as non-profit organisations, but there is an increasing number of commercial milk banking models. Commercial HMBs pose an ethical issue with regard to human rights, vulnerability, equity and fairness, quality assurance and safety.

In terms of structure, milk banks may be centralised – with one large, centralised milk bank which distributes milk within a region – or decentralised. Here, smaller milk banks are distributed across the region. The facility may be community or hospital based; and it may be independent from the larger healthcare system, i.e., functioning primarily as a milk processing unit, or integrated into the healthcare system, for example being part of larger initiatives to support breastfeeding and human milk feeding. Brazil is a good example of an integrated system. In Brazil, milk banks are called 'houses of lactation', reflecting the larger aim of milk banks in protecting, promoting, and supporting breastfeeding.

Performance Indicators

To achieve greater impact in improving infant health, it is critical for milk banks to reframe their performance indicators to reflect an integrated health system that seeks an exclusively human milk diet for infants as an indicator of success, with linkage to specialized lactation support for mothers of vulnerable newborns. DHM should be a tool supporting the larger goal of improving infant nutrition by facilitating an exclusive human milk diet, without usurping the role of MOM or breastfeeding support measures. This goal is reinforced when a government aligns its policies to promote BFHI and to enforce the International Code of Marketing of Breastmilk Substitutes, so that milk banks are implemented appropriately within a larger framework of promoting the appropriate use of human

milk. This purposeful integration of human milk banking within nutrition and newborn programming, policies and implementation is recommended over purely measuring the volumes of DHM collected and provided.

Sustainability

Sustainable funding of milk banks is often initiated by passionate advocates aiming to improve the quality of newborn care at their hospitals. Start-up funding is often raised through personal fund-raising efforts, and these milk banks may be independent of the health system and unknown to the Ministry of Health in that country. The result is a milk bank that is neither adapted nor integrated into the larger health system. A more systematic process, involving government bodies during the planning process, developing guidelines suited to the local system, identifying barriers through formative assessments, understanding the communication requirements of the local setting, and having operating procedures responsive to the local setting, is more sustainable in the long run.

Regulatory Frameworks and Oversight

Human milk itself is classified very differently around the world, which leads to differences in the legal frameworks governing human milk use as well as differences in operating procedures and challenges in utilizing a unified regulation system for human milk. Countries tend to advocate for the benefits of HMB in the same manner they classify human milk. The most common classifications are:

1. As a food: This results in lower overall regulatory costs, but may involve some unnecessary requirements, for example requiring food labels and declarations (e.g., stating that 'this product was not processed on equipment that processes peanuts').
2. As a Medical Product of Human Origin (MPHO); previously classified as tissue: MPHOs tend to be regulated more tightly with increased trust in the resultant product.
3. As a nutritional therapy
4. Undefined – this usually serves to indicate that human milk is in a class of its own and does not fall into the previously defined categories. The regulations applied to it may then be a hybrid based on several suitable categories.

There is no global oversight of human milk banking. More established organisations, such as EMBA and HMBANA, are looked to as leaders in the field, especially because of the resources, technical assistance, and mentorship they provide. Brazil is one of the leading countries with regard to human

milk banking, with a national network of HMBs. Brazil also exports this model, providing outreach to other Portuguese- and Spanish-speaking countries in a programme managed by the Ministry of Foreign Affairs. They have since provided support to at least 25 countries.

Knowledge Gaps

There is a long list of knowledge gaps around policy and regulation, technology and innovation, the impact of human milk banking systems on newborn health, the medical, technical, social, nutritional and financial issues pertaining to human milk banking, optimising the quality of pasteurised DHM, and developing implementation models for LMIC (low-and middle-income country) settings, where guidance may be helpful. These are further elaborated on in the full background document. The underlying question of why mothers' own milk is often not fully available remains, and at the individual level should always be addressed to minimise the need for DHM.

Points of Discussion for Global Overview and Status of Human Milk Banking

1. Managing Complexity

Understanding the practice of milk banking internationally is a complex endeavour. One way of simplifying the process of understanding the safety issues related to HMBs is by developing a clear hazard profile of DHM. Every country that banks DHM should recognise the clinical hazards of DHM and apply a set of mitigating processes such that the resultant risk to their intended recipients is acceptable. Countries may have entirely different processes to manage the same universal hazards based on what is acceptable to their population. Guidelines that embrace differences in practice, reference commonalities, and outline the minimum and maximum quality standards that need to be met, are necessary. There is a danger of the 'pick & choose' approach – indiscriminately putting together parts of different HMB processes to then create a 'new' one – which runs the risk of disconnecting the practice, the process and the hazard that is being managed. A hazard that should not be ignored is the use of DHM when MOM is available, or would be if optimal lactation support practices were in place. Denying infants their MOM because of the ease of availability of DHM in itself presents a hazard, albeit a lesser one than for other alternatives.

It is important to look at the optimal use cases of DHM, and determine the necessary standards for safety and quality, while providing room for different systems to operate. On the other hand, there should be awareness of how DHM might be used inappropriately. Both gathering information about

the use and misuse of DHM and determining minimum standards is difficult when there are knowledge gaps, sometimes perpetuated by the lack of funding to do research in this area. Investing in both empirical and qualitative research, and in the development of DHM related technologies, may be the key to providing solutions for current challenges. For example, the current pasteurisation process in use in HMBs was developed for bovine milk – but investment in a pasteurisation system developed specifically for human milk may result in a higher quality product post-pasteurisation. Keeping this in mind, while establishing minimum standards, is critical; it is also important that any guidance/regulations developed are not so specific as to impede newer and better technologies and information to improve processes.

While acknowledging the complexities of implementing an integrated milk bank, the operational aspects of an HMB at the level of the hospital need to be simplified in order to be feasible in a wide variety of settings, including low-resource settings. In some hospitals in low-resource settings of South Africa, milk banks have been set up safely using low-cost pasteurisers with little water and electricity. Simple methods – such as building an incubator to plate and incubate milk on-site and discarding milk that has any growth post-pasteurisation – allow the implementation of milk banks at a low cost while maintaining safety standards. At the same time, over-simplified guidelines which point out hazards and which lack clear guidance on appropriate management may prove to be ineffective, as countries with limited resources may not have the capacity to work through these issues.

2. Terminology and Definitions

MOM and DHM vary in their composition and there can be a significant variation between DHM products. Therefore, it is important to specify whether DHM is raw, pasteurised or otherwise processed. It would be helpful to clarify the profile of different types of human milk and its appropriate use – for example, the quality and safety category level of DHM required for a very low birthweight infant coming off parenteral feeds is different from DHM required for a low-birth weight infant with no other complications.

Human milk is unique and we are still discovering what should constitute human milk of the ‘highest’ quality. In the past, it was assumed that no bacterial growth meant that the DHM was of high quality, but the current discourse challenges that, questioning instead whether destroying the microbial content of milk reduces its quality. It is important to clarify this difference between safety and quality when applied to human milk.

There are concerns over the term ‘donor’ being used misleadingly by commercial entities that buy and sell human milk, and whether this should be permissible.

3. Regulation of DHM

Given the complex profile of DHM, existing regulatory frameworks are imperfect proxies for its regulation, with DHM overlapping into various categories within the legal framework. It may be useful to fit human milk into existing structures with funding and support, so that the outcomes expected are not compromised. In terms of global guidance, it would be helpful for countries to have a set of principles to apply before deciding how to classify and regulate DHM.

4. Integration of HMBs into Health Systems and Lactation Support Frameworks

In South Africa, being a ‘Mother and Baby Friendly hospital’ is a prerequisite to opening a milk bank. This is a good way of ensuring that milk banks are set up in places where mothers are supported, and that DHM is used appropriately.

In certain circumstances, DHM may become a substitute for MOM. This occurs when, for whatever reasons (e.g., maternal death, illness or adoption), the mother is unable to provide her own milk to her infant. In some settings, DHM is inappropriately used. For example, infection control measures can involve prohibiting parents from entering NICUs, holding their babies or having skin-to-skin contact when their babies are at their smallest and sickest. Mothers in these settings may not have access to the same breast pumps that donors have, or a mother might be admitted to another unit in the same hospital without a transportation system in place to ensure her expressed milk reaches her infant in another ward. Although there is an effort to provide human milk, the emphasis is not on supporting MOM feeding. By the time infants are better and moved to a step-down unit with greater parental access, optimal lactation is hindered, maternal milk provision potentially compromised and the sepsis-preventing and other benefits of MOM lost. In such settings, since hospitals use human milk instead of formula, they justify that the use of DHM is consistent with WHO guidelines, when instead DHM is being inappropriately overused.

Family participatory care in the NICU involves parents extensively in the care of their high-risk infants. This may be facilitated by housing mothers close to the NICU and enabling fathers to transport MOM to the NICU, addressing one of the barriers of transporting MOM to NICUs. NICUs will need to ensure

that bottles of MOM are properly labelled with identifiers, time and date stamps, and that they have an effective process for handling MOM once it reaches them.

The development of guidance looking at the processes required to provide specialised lactation support for mothers of neonates in critical care, how to acquire and store MOM, embedding milk banks within a lactation support programme to ensure a comprehensive approach is implemented, and the logistics for handling milk thereafter for storage and transport (if mothers and babies are separated) would be helpful in facilitating these processes.

5. Reconceptualising Pasteurised vs. Raw Milk Systems

The use of pasteurised and unpasteurised DHM within a single healthcare system does not need to be mutually exclusive. Some milk banks in Germany operate a dual system using both PDHM and unpasteurised DHM. Unpasteurised DHM is reserved for the smallest and sickest infants, and PDHM for babies who are less ill. Although this may seem counter-intuitive initially, the hazards are managed so that unpasteurised DHM undergoes additional donor screening and meets stricter microbiological testing criteria. DHM that does not meet the criteria allowing it to be safely used as unpasteurised DHM may then be pasteurised and provided to other infants.

6. Unique Complexities of DHM Impact on Mother-Infant Relationships

Understanding how DHM could affect the relationship between mother and infant is crucial and should be reflected in guidance related to HMBs. Some open questions include whether DHM is only appropriate when mothers can simultaneously be present and have access to their infants, or when optimal lactation support is also provided, so that mothers would be able to produce optimal volumes of their own milk in the long run.

In determining standards for blood donations and transfusions, clinicians were actively engaged in determining how blood should be used, and in developing standards about when blood should be ordered so as not to disrupt natural processes and resources. There is also always a risk when using a product of human origin, and breaches of safety may happen. Working closely with end-users, neonatologists and other related health professionals is crucial to ensure there is no disruption of breastfeeding possibilities.

Overview of Operating National Tissue Banking Programmes

Gillian Weaver & Marisa Herson

For a long time, DHM was mainly classified as a food since babies are fed with it. However, with additional knowledge about human milk came the realisation that it also has characteristics of a nutritional therapy and of an MPHO. Appropriately classifying human milk – as a 'food' or MPHO remains a challenge. The significance of considering DHM as an MPHO lies in its human origin and the medical aspects of DHM use. DHM is used to improve health care, and there is a consensus in practice about the common ethical values between DHM and other MPHOs. Common ethical issues affecting both DHM and other MPHOs involve the need for equity of access, avoidance of socioeconomic inequalities, and the increasing trend of commodification translated in its commercialisation. While DHM has been established as an appropriate nutritional source for low-weight babies, safety and quality considerations resulting from its human origin and manipulation may suggest some benefits if DHM were to be regulated as an MPHO.

Ethics

As per the WHO Principles in Human Organ, Tissues and Cells (inclusive of DHM), donation should be, overall, an altruistic act, with accepted reimbursement made of 'reasonably incurred' expenses, albeit this definition can be blurred sometimes. The 'no trade' concept is often embedded in national legislation, but in reality, this is defined by practice. In some countries, plasma donors are paid by the volume of plasma donated, semen donors are also reimbursed, and gamete donors are often sourced in developing countries, with husbands bringing their wives to donate ova as a source of income for the family. There are many grey zones in the practice of reimbursing reasonably incurred expenses.

There are also clear inequalities between those who can donate and those who can receive DHM. Although it was not so apparent when milk banks were first initiated, the possible exploitation of the women donating milk is a challenge that needs to be addressed. There is also a clear lack of equity of access. This can happen locally within a hospital, when individual decisions by healthcare staff result in inconsistencies in the distribution of DHM, or at the regional level, based on the level of supplies and the sustainability of milk banks.

The commercialisation of human milk and the ability to make an inappropriate profit impacting on accessibility to DHM is an emerging issue, and an increasingly widespread one. It is important to consider the circumstances, if any, wherein for-profit trade of DHM might be acceptable.

The ethical considerations surrounding DHM have only recently gained traction. It is unfortunate that ethics has not been regarded more highly in this field. For many involved in human milk banking, the focus has been primarily on ensuring the safety and quality of DHM. With growing experience in milk banking, the ethical ramifications have become more apparent.

Policies and Legislations

With regard to policies and legislation, what are common among all MPHO programmes are concerns about risk, and a risk-mitigating approach. These are reflected in the agreed importance of frameworks addressing quality and safety, and have stimulated work in developing standards for MPHOs.

As it is unclear how DHM should be classified – as a food or as an MPHO – it is also then unclear how DHM should be regulated. Classifying DHM as a food distances it from the benefit of important discussions on ethical issues and its human origin. To add complexity, in some countries such as India, human milk is classified in a class of its own, with a separate set of legislation being developed around it. Specific standards set by professional organizations do exist for HMBs, but their adoption is ultimately voluntary and there can be a lack of transparency around whether they are adhered to in practice. Therefore, it is likely that some HMBs are non-compliant with professional standards, including ethical standards.

To curtail risk, there is the trend to adopt standard practices that will potentially manage all detected risk. While very high-level standards based on good laboratory or manufacturing practices can be developed, there can be issues when the standards are set too high, imposing an excessive financial burden in implementation for institutions or milk banks that are already struggling to exist.

Finding the balance between the minimum required standards and the aspired optimal levels of quality and safety is key, so that they are beneficial without being unreasonable. In creating policies and legislation, it is also important to keep in mind harmonising standards while not stifling practice through increased costs.

Regulations may not necessarily be willingly accepted by everyone; nevertheless, they may be welcomed because they ensure that the system is transparent and that products delivered meet minimum quality and safety requirements. However, rather than being solely established and imposed as a legal requirement, adherence to promoted standards can be improved when they are created with strong input from the relevant professional associations, are adopted voluntarily and are self-monitored.

Access to donated milk, as to other MPHOs, will remain inequitable unless there are policies and appropriate governance in place that understands the demand, ensures sufficiency of supply, and provides for sufficient funding arrangements in order to allow the system to function. While it is useful to obtain a government grant to establish a milk bank, such milk banks might struggle financially in the absence of further government support, unless the subsequent operational model minimally and effectively recovers the fixed and variable costs incurred in recruiting and selecting donors, and processing, storing and distributing the DHM.

Commercial practices may have a negative impact on equitable access. Inducements to donors and aggressive marketing tactics jeopardise the altruistic ethos of any MPHO banking programme. Uncapped profits driven by shareholder interests will ultimately impact access when recipients are unable to afford higher product prices. These aspects should be included in legislative and policy considerations.

Donor Selection

There is a large amount of concern regarding the risks involved in donor selection and preventing disease transmission via any MPHO. MPHO donation programmes screen donors extensively with respect to medical issues, from those affecting the quality and safety of the donated organs, tissues or cells, to issues impacting donor welfare. Although it is accepted that the risk of MPHO use is never zero, instituting overzealous safety measures may result in unnecessary ’donor exclusion’. To avoid this, exclusion criteria should consider both the general and tissue or cell specific criteria and the final product risk. For DHM, this may consider the specificities of microbial, viral and drug transmissibility.

The donor selection procedure usually includes a number of elements that jointly aim to reduce overall risk and help ensure that selection outcomes are consistent. While the details may differ slightly based on the requirements of different tissues and cells, donor selection programmes incorporate information on the importance of sharing personal and medical details as part of the

donation informed consent, a medico-social interview and physical examination, blood screening, repeat serology (in most living donations), and relevant ancillary investigations. There may also be additional screening requirements that are environment-specific (for example, Zika virus in Brazil) and tissue cell-specific (such as sperm motility or quantity per sample). Beyond disease transmission or drug exposure via the donor milk, an additional challenge for milk banks compared to other tissues is weighing the impact of donation on the donors' own milk production and on the feeding choices for the donors' own babies. The ideal donor recruitment procedure for HMBs that specifically supports MOM feeding alongside donation has yet to be established.

Donor Registries

Donor registries have been extremely useful in certain MPHO programmes and have clearly contributed to the success of bone marrow donation programmes. Collating data of utilisation and outcomes allows an understanding of donation trends, supply and demand, and medical capacities which ultimately contribute to improvements in technical and medical practices.

However, maintaining a donor or utilisation registry is a resource-intensive process both in terms of labour and finances. It is important to understand the exact purpose of the records being kept, and how this data will be used. It is also important that the registries are kept updated, with relevant and coherent data being supplied on an ongoing basis, so that it does not become obsolete. There are many donor registries with high rates of non-conversion, i.e., where people initially register their intent to donate but fail to update the registry of changes in their details, and are then uncontactable when called upon. For these reasons, registries also require appropriate governance.

It is difficult to motivate ongoing voluntary contributions to a registry in the absence of any clear or direct benefit to those contributing; therefore, the effort should be organised and responsibilities shared among all stakeholders. The Australian Cornea Registry is an excellent example of a well-functioning registry, financially supported by the Australian government and a Perpetual Trust Fund (Flinders University), with information on utilization provided by eye banks working in collaboration with clinicians who provide regular feedback on utilization and outcomes.

There are no known registries of potential donors to milk banks although, whilst the essential immediacy of most human milk donation reduces the value of being able to contact a person who registered previously, understanding aspects of why donors are ultimately accepted or deferred would be helpful. The processes in milk banks are rarely digitalised, although this is growing,

hampering the collection and organisation of data, and limiting data-sharing between institutions and countries.

It is not generally known where or if any data on potential donors, or outcomes of donations is being collected by milk banks, and when data is indeed being collected, it is not known if the definitions of the parameters being measured are shared across milk banks. For example, for one milk bank, a 'discard rate' could refer to milk discarded because it did not pass microbiological scrutiny. For another milk bank, the 'discard rate' could refer to all milk discarded for any reason, including milk that has passed the expiry date. The lack of coherent definitions and systematic data collection, together with the low level of data sharing, prevents the effective identification and solving of problems related to human milk banking.

Public Awareness and Donor Education

Public awareness about donations varies significantly between MPHOs. Organ donation is best known among the public, followed by bone marrow, cornea and gamete donations. There is overall poor public awareness on tissue donation, of which milk banking could be considered a subset. The reasons for the lower levels of awareness range from limited funding to launch effective educational campaigns towards donation, to lesser political lobbying towards expanded levels of interest in tissue donation and transplantation. There is no standard formula when it comes to raising public awareness. Communication strategies differ based on the MPHO in question, the financial resources available and competing healthcare priorities, but experience has shown that it is best if messages can be simple and clear and promote some form of action. On the other hand, misconstrued messages or inappropriate incentives could lead to the unacceptable commodification of the MPHO.

In the UK in 2014, milk banks were described as the nation's 'best kept secret' (Weaver, 2015). Most people believed that milk banks had been closed. Low levels of public awareness can be addressed very easily these days using social media, while being mindful of cultural sensitivities and the appropriateness of the messaging. Mothers are generally very experienced in using social media. While there can be difficulties stimulating interest around non-mothers, amongst families, especially those planning to have children, milk banking is immediately relevant to their needs. The use of social media has led to UK milk banks becoming much more recognised since the 2014 survey, with surpluses of donors and milk now being reported by most banks.

Quality Assurance

Quality assurance and safety is imbued in all MPHO programmes and is key to managing the risk of issuing a product that does not comply with expectations with respect to quality and safety. If the agreed minimum standards of quality and safety cannot be achieved, a decision needs to be made on whether to follow a different set of processes or whether the MPHO programme should be in operation at all. Quality management systems should be in place to monitor that relevant protocols and work standards are followed. Through documented procedures, they outline, direct and record each significant step in the MPHO programme – from sourcing to the release of the MPHO for utilisation. As an example, with understanding and controlling environmental contaminants that may impact the quality of the final products, it may be recommended that they be handled in Grade A environments (e.g., laminar flow cabinets) by trained and competent staff in the execution of any adopted protocol. Although human milk may have been collected at home or on a hospital ward and so outside the milk bank's sphere of supervision, it is incumbent upon milk banks to consider similar measures so as to protect the DHM from any additional contamination.

As part of the quality management systems, there should also be a quality assurance programme – validating and verifying that the entire operation conforms to the decreed standards and that the expected outcomes are being met. This would involve engaging both internal and external auditors. The current reality of milk banking is that, despite the efforts applied to safeguard DHM, quality management systems are not in place or there are identifiable gaps.

Operational Models and Funding

There is no universal operational model that reflects the realities of all milk banks. The best operational model would be one that allows donation, banking and utilisation to occur according to ethical values, following the best possible safety and quality standards, and delivering targeted results according to socio-economic realities and funding possibilities. Milk banking programmes should be planned so that these essential targets are reflected in their basic operational models.

The entire cycle from donation to provision to recipients, underpinned by dedicated governance, regulatory oversight, infrastructure and a competent workforce, requires an appropriate funding model. Funding models may vary from on-going investment by health departments to operational sustainability generated through cost recovery models. As with other tissue banks, HMBs are also likely to engage a range of public, private not-for-profit, and for-profit players or service providers in

their daily operations (for example, by engaging a courier service to deliver the DHM). There must be a clear understanding of the role of each entity involved and policies surrounding their engagement. A 'standard' or fixed budget for running a milk bank is difficult to establish because of the diversity of milk bank operational models and their varying scales around the world. Ultimately, what constitutes the most suitable model is likely to vary by location, funding arrangements and turn-around. Nevertheless, as for any other tissue and cell banking operation, whether public or privately funded, for-profit or not-for-profit, it is important that milk banks are run efficiently and have sound business plans in place. Minimally, to honour ethical expectations, HMBs must respect donors and ensure the best possible outcomes for potential recipients.

Infrastructure and Human Resources

The infrastructure and human resources available to milk banks can similarly vary from a sparse room at the back of a hospital to large, stand-alone, well-equipped and well-staffed facilities. What is important is that the facilities should fulfil their purpose and enable compliance to the quality and safety standards.

If a milk bank starts small, it is important to be aware of and plan for future growth. Operational models can harness structures that already exist – for example, making use of the capabilities and resources of other tissue banks within the same hospital and synergistically streamlining workflows where possible. In the absence of specific guidance about the layout of milk banks, turning the initial designs into a dedicated milk bank facility remains very challenging. However, commonalities with other MPHO manufacturing as far as environments and flows are concerned, can be used as roadmaps.

Staff should be available in adequate numbers, be adequately trained and competent at their required duties. Where milk banks rely on minimal staffing levels, the challenge of maintaining the operations of the milk bank in the event of staff leaving, sickness and other types of leave must be accounted for in the business plan. Although the provision of certain services required of the milk bank may be contracted to third parties, the milk bank retains final responsibility for the quality and safety of DHM, and training and competency assessment are important elements of this.

Biovigilance and Evaluation Outcomes

Most frameworks and standards for MPHOs include procedures for biovigilance and the evaluation of outcomes. These involve understanding where products are distributed to, and how they are used. To enable traceability and biovigilance, as with other MPHOs, each distributed DHM unit must be uniquely identified so that it can be traced back to the donor and from the donor to each recipient. The potential for effective national and international traceability of human milk products has been improved by the inclusion of human milk in the ISBT 128 coding system. The not uncommon practice of pooling milk from multiple donors poses an additional challenge for effective traceability as milk from several women may be pooled and then distributed to a number of infants. Milk banks need to carefully consider that this makes the recall of a non-conforming product or batch a much harder task, posing increased risk to potential recipients.

The recall and reporting process of an adverse event needs to be established as part of the regulatory framework, including responsibilities and reporting pathways to the regulatory authorities who will have the role of following up to ensure suitable responses were enacted. These events and mitigating measures should be further shared within the professional associations for educational purposes and the improvement of standards and practices.

Similar to other established outcomes registries or platforms (e.g., NOTIFY Library), it is worth looking at the benefit of national or global DHM specific outcome registries, in particular at how adverse events should be notified and with whom they should be shared. Often adverse events and reactions can be only captured within the clinical setting, beyond the ability of a milk bank. Open communication channels among all stakeholders are crucial.

For other MPHOs, maintaining outcome registries has been an important tool for detecting non-conformances and cumulative events, and the improvement of practice. For example, a relevant non-conformance in the way tendons had been processed by an establishment in the UK was detected in an outcome's registry on account of the cumulative reporting of graft failures over a five-year period.

Points of Discussion for Overview of Operating National Tissue Banking Programmes

1. Issues with Procurement and Processing Procedures

There is a small number of manufacturers of equipment for milk banks and the equipment may vary to such an extent as to not be easily comparable. There is a virtual monopoly on some equipment, notably pasteurisers, and validation guidance has not been used to create international standards, although recommendations for pasteurising equipment are available (Picaud & Buffin, 2017).

In some countries, there is also no local equipment maintenance support. This poses a challenge for ensuring equal processing procedures are followed, as is often required by health departments and regulatory bodies. Some milk banks have solved this by designing and building their own equipment. Another solution would be to look for alternative methods of achieving the same results using common items (such as using laboratory water baths and blast chillers to provide the required heating and rapid cooling of the milk). If alternative solutions are being utilised, it is important to validate that using these methods delivers the required quality standards. For as long as the optimal quality standard of DHM remains undetermined, questions around the required end-product quality and safety levels will complicate the selection or designing of appropriate equipment that meets those needs, is affordable and can be locally maintained and validated to meet required performance indicators.
Validation guidance is available as part of the PATH HMB Toolkit appendices (1: Verification Protocol for a Holder Pasteurization Device, and 2: Performance Specification for a Holder Pasteurization Device.) (PATH, 2019a)

2. Human Resources

Personnel with key roles in the HMB are required to take responsibility for the operations of the bank. Staff may work on a part-time or full-time basis, but there should always be enough trained and competent staff to keep the programme running. In a tertiary level hospital, there may be staff already available on a part-time basis, and part-time staff may be a more practical human resource strategy. This may also be more acceptable to authorities, as it tends to be more cost-effective. Having a dedicated staff can sometimes be a challenge. Time and resources are required to train a select few people intensively, who may then be rotated to other departments. It is possible to train staff in conjunction with other training programmes to limit additional costs. While determining staffing issues should be done locally, accounting for the possible rotation of staff should be part of the human resource planning. It is important ultimately to ensure staff are competent according to defined standard operating procedures, and have the specific skills needed for the HMB.

3. Physical Layout of HMBs

It is important to identify the purpose of the human milk banking space, its location, and its surrounding environment. Identifying the scope of activity of the milk bank would help decide on the kinds of spaces that are needed – for example, a reception area, a group counselling area, a hand washing station with changing area and shower where required, and a milk expression and collection area may all be desired, in addition to milk storage, milk processing, milk distribution and administration areas. It is important to determine the minimum standards that are required in defining the layout. Having a single room for all processes to be done would be disruptive to safety procedures and may compromise the quality of products. In determining the layout, it is useful to consider the type of the milk bank (for example, is it an institution in isolation, or integrated within a hospital – in which case it may be useful to have the milk expression room in the maternity ward rather than in the milk bank itself), and the surrounding facilities (for example, sharing the reception area with other departments). It would be useful to have co-operative or technical visits, where others with experience in milk banking give input into simple but crucial questions about the HMB's design.

4. Registries and Data Collection

If a web-based registry is being developed, integrating it with other related health management systems could also be considered. Examples of this include lactation management and population-based data (with the total number of pregnant women and Caesarean deliveries). In identifying the different types of data that should be integrated into the registry, determining the purpose of the data captured is crucial to ensuring meaningful outcomes. Capturing data related to the activity of milk banks is only truly useful if infant feeding data is also collected, especially related to vulnerable infants in hospital.

5. Exploitation and Ethical Issues

Milk banks have a role in preventing exploitation and mitigating the ethical issues related to DHM and they are reliant on global and local policies, which currently range from being, at best limited, to at worst non-existent, around human milk. A call to action for equitable access to human milk for vulnerable infants from the Oxford-PATH Human Milk Working Group lists ethical considerations to shape key actions as well as suggested global and regional actions to achieve equitable access to human milk. In this call to action, global, regional and country level policy and regulatory bodies are

called to establish governance mechanisms and enact legislation for the safe and ethical use of DHM in a way that, very importantly, also protects, promotes and supports breastfeeding.

Little is known about the motivation, experience, and characteristics of human milk donors. It is important to consider whether the DHM is surplus to the baby's requirements, whether this should also consider the baby's future requirements, and what alternatives are available for surplus milk apart from donations to HMBs. Many mothers donate milk because they do not have the storage capacity for the milk they have pumped for their babies, or electricity or facilities at home for its safe storage. It is important to consider the alternatives for them, and not to deprive women and babies of milk that may be useful for themselves. However, this also presents a conflict of interest. It is fundamentally important for larger agencies (such as government health departments or food departments) in their national policies to also reflect issues related to and preventing the exploitation of women, and to have overarching authority over the milk bank. There is often a commitment to monitoring in relation to quality and safety. The same rigour is rarely applied to monitoring for exploitation. In determining guidance, we should consider how monitoring and regulation for exploitation can be operationalised.

6. Quality and Safety

There is a tendency for a 'safety creep' in MPHO processes, where it is difficult to resist adding an additional action based on additional safety. Safety is a subset of quality and is especially important when it impacts an already extremely vulnerable baby. At the same time, there should be a balance between safety and reasonable actions to achieve a safe product and outcome given the health systems, risks, burden and resources. With MPHOs, there is an acknowledgement that no matter how much we do, there is always a residual risk. A completely safe DHM product would be almost impossible to issue as the available volumes would be so greatly curtailed. For example, testing for every possible contaminant, including environmental, would increase costs to the extent that most milk banks would be unable to operate. How then do we determine how safe is safe enough, and what safeguards are sufficient?

From a microbiological safety point of view, mother's milk is unique amongst MPHOs in that there is usually a critical control point of heat treatment with pasteurisation. At the same time, the effects of remnant toxins, spore-forming bacteria, lipid-oxidation and other processes may remain even post-pasteurisation. Pre-pasteurisation testing of milk offers quality assurance of the collection process as it can identify issues with the expression, handling and storage of the milk all of which may allow the

introduction of contamination or uncontrolled microbial growth. However, it also necessitates additional costs that may be prohibitive, the need for tests that may not be locally available, and inevitably increases the discard rates due to milk not conforming to standards that would not be apparent from post-pasteurisation tests alone.

With many unanswered scientific questions, it is difficult to determine with certainty whether an action or a process is harmful. The easiest thing to do then would be to halt that action in the name of safety, but again, this would preclude DHM from being used. It is important to adequately control for quality, testing representative samples in a rigorous way to ascertain that the results that are being aimed for are indeed being achieved. This needs to be done with the best technique for the resources available to the milk bank, so that the DHM is as safe as possible, but not prohibitively so.

Doing as much as possible with regard to safety allows a milk bank to determine the cause of an adverse event more accurately when it occurs, and to review and improve its own processes. Considering the risks associated with the alternatives to DHM is helpful in determining what the acceptable boundaries of safety are. This benchmark varies based on location.

Targeted Discussion: Identifying Knowledge Gaps and Challenges in Human Milk Banking Based on the Background Reports and Presentations

In defining the need for international guidelines, it was necessary to identify the specific areas in which guidance would be useful, keeping in mind that this would be guidance at the global level.

Products developed by the WHO are developed in consultation with member states, with issues taken up at the governmental level. The products developed depend on the specific needs of the industry in question, and the developmental process varies depending on the type of product. Developing technical guidelines is a time- and resource-intensive process, requiring a thorough review of the current practice. There is a need for flexibility to take into account the results of future research (e.g., in processing methods) and to allow for pilot studies. Other initiatives could be just as beneficial and quicker to develop – for example, creating a policy brief. To develop a meaningful and timely product, we should first ask what are the most pressing issues in HMBs that require a response.

Classification of Human Milk

Although some countries consider human milk to be a food product, DHM is screened and contains intrinsic elements like other MPHOs. There have been member state requests for the MPHO framework to include DHM. The further development of DHM would be part of the implementation of specific products within the WHO's MPHO common framework (WHO, 2017). However, at present, member states' efforts tend to focus on more conventional MPHOs such as blood, plasma and organs.

There may be a strategic advantage for DHM being assigned an MPHO label. Health programmes tend to receive more support than food programmes, including in considerations around policies and with regard to ethical approaches. On the other hand, classifying DHM as a tissue may impose challenges based on current policies surrounding MPHOs. For example, if DHM was classified as a tissue, it would be prevented from crossing borders in certain states in the U.S.A, preventing its distribution based on current operating models. Navigating these local regulatory issues divides opinion on how DHM should be most practically classified.

Another way of considering the classification of DHM would be comparing DHM to its alternatives and considering how these are classified. From a regulatory standpoint, DHM is currently more closely comparable to other forms of enteral feeding (as opposed to parenteral nutrition, which is more

processed and more overtly medicalised). At the same time, the benefits of DHM lie not just in its nutritional value, but in its active biological and human components, which serve a medicinal function. DHM might also be applied therapeutically in other ways – for example, as a topical application in burns dressings for infants, in which case it is not utilised for its nutritional value at all. It is important in keep in mind that there may be future uses of DHM that are as yet undetermined.

The provision of DHM may also be framed as a clinical service. This would classify it as a health provision and require a definition of the settings in which it should be provided and its criteria. It would also then fall under the purview of the health authorities, although it may be simpler to regulate.

There are advantages and disadvantages in any classification system (PATH, 2013 pages 21-24). Although coming up with a unique framework for DHM may solve these issues, navigating multiple legal systems would be a complex endeavour.

Global guidance on classification should not be unnecessarily limiting. Countries should have some guidance on suggested classifications but should also retain the option of whether to follow this, based on their particular context. It is of greater importance globally that minimum requirements to achieve are agreed, and outcomes of safety and quality are reached. The terms ‘quality’ and ‘safety’ need to be clearly defined when referring to DHM. The next step would then be defining both the upper and lower limits of acceptable standards of quality and safety. Clarifying the classification of DHM as food or tissue would affect the regulation of the DHM, but this could be independent of the consensus on the requisite quality of the end-product. Milk banking in Australia is a case in point, where there is an acknowledgement that uniformity in terms of classifying DHM is not possible due to differences in the legal systems operating across different states. However, there are unified regulations addressing quality and safety issues in terms of the end-product of DHM. The emphasis is then on achieving a particular outcome across state boundaries, rather than insisting on a homogenous legal classification. What might be useful in terms of guidance in achieving these outcomes would be elaborating on the important elements or processes that should be in place in the relevant classification systems if a country chooses to classify DHM in a certain way, whether as a food, an MPHO or by adopting a new classification (if that provides a better balance between regulation and equitable access).

Recognition of the Importance of DHM

Further to the issues of quality and safety, there is recognition that the majority of milk banks are currently being established in a non-standardised or unregulated manner. There is growing public recognition of the importance of human milk. It could be surmised that the absence of regulations for milk banks may encourage milk sharing in an informal manner, with its absence of quality and infection controls. This may lead to adverse events in which human milk is implicated and may then be detrimental to future DHM use.

There is a consensus on the need for an overarching – and appropriate – governmental regulatory role for HMBs to ensure safe, quality and ethical processes are implemented. A proposed guidance could involve the WHO clarifying the differences within HMB models and processes, and providing an analysis of the different possible options and case studies from various countries. This would cover the main components of human milk banking such as donor recruitment, donor screening and safety, quality and operating models, technical aspects of DHM processing, the perspectives of end-users, and ethical concerns. This would also provide a reliable guide as a basis for countries looking to start their first milk banks.

Lack of Data around HMBs

Developing guidance is currently limited by the lack of data around HMB practices and a defined 'need' for DHM globally. A major gap is that most research has been performed in high income countries. At present, clinical evidence supports the use of DHM for the prevention of NEC and for infants with very low birth weight, whereas other potential areas to use DHM have not been thoroughly examined. To further complicate the lack of data, human milk is often used as an undifferentiated term in studies, referring to both MOM and DHM, without recognition of their differences. This limits the interpretation of the available data. Part of any guidance being developed might involve clarity on the limited evidence-based benefits of DHM for the end-user, indicating whether this limitation exists because of a lack of studies showing benefits, or whether studies were indeed done but did not show a benefit.

The WHO maintains a Global Observatory on Donation and Transplantation (GODT) of organs, created in collaboration with the Spanish government. It may be useful to replicate this with milk banks to collect data and fill knowledge gaps. The GODT sends an annual questionnaire to all member states so that there is a global database of annual activities. The questionnaire form also clearly states the

definitions of everything being asked for, so that definitions are harmonised, and data is made comparable. This transfers the responsibility of data collection to member states, and usually obtains a response rate of 80%. Milk banks could similarly be included in a registry under the oversight of the WHO using a standardised data collection form. An overarching global body or global alliance has been under discussion for years among the leadership of HMB groups, and such a registry might be the first step in creating such an alliance.

One challenge that a WHO-led registry would face is pushback from countries on the immense volume of data they are already requested to provide to WHO-led initiatives, of which HMB and neonatal feeding would be just one component. Limitations in the capacity to manage data collection by countries may also affect the quality of the data provided, even if it could be supplied. It may be more practical to request information that governments are already collecting for their own purposes and which would also serve HMBs. An example would be capturing neonatal mortality in NICUs, since neonatal mortality is a statistic routinely captured by health departments as one of the SDGs. Feeding data for this population is not yet routinely captured. Another alternative is working with third party sources such as NGOs to collect the required data. There is much potentially relevant data already being captured, for example global infant feeding indicators, that has not been purposefully designed to record the target population of HMBs, namely vulnerable infants. It may be wise to develop a working group focused on defining the indicators and data required, and determining if and how indicators from data already being collected can be improved to meet the data needs of HMBs. This would enhance the data collection already taking place to inform human milk banking activities without over-burdening countries.

An alternative to a global database is collecting data at the regional level. In documenting early essential newborn care in the Western Pacific Region, member countries collate data, then nominate a person to form an independent review group validating the data of the other countries. The findings are then published. Areas where data are needed but lacking are highlighted, and actionable recommendations are included, for example, by advising if this data should be measured over time in a national survey or in a second round of data collection. Collecting data on this smaller scale allows meaningful representation of regional perspectives.

Ethical Considerations

Considering the right of the child to human milk, as included under the human rights framework, is fundamental to all discussions around the ethical framework of human milk banking and the availability and use of DHM.

DHM is unique as a product in that the donors and recipients are both mother-infant dyads. This should be kept in mind when considering quality, safety and ethical aspects, such that the impact on both members of each dyad should be carefully thought about. For example, when going beyond the interest of the recipient infant to stay safe from transmissible diseases, it is also necessary to consider the interest of the recipient mother in being able to provide long-term human milk feeding for her infant.

There is strong evidence of the benefits of MOM for sick babies and it should always be prioritised. Inadequacies in breastfeeding and lactation support need to be addressed in tandem with the need to supply DHM. Milk banking should be placed in the context of supporting an exclusive human milk diet, including improving access to MOM, such that it supports breastfeeding and lactation outcomes rather than supersedes or undermines them.

In an optimal feeding systems framework, DHM would only be used when needed. However, access to DHM when mothers are unable to produce enough of their own milk can be problematic. Even in resource-rich countries such as the US, there are significant disparities in the use of both MOM and PDHM. In hospitals serving lower income families, the rates of human milk feeding are low primarily because mothers are not informed about the benefits of MOM, and lactation support is inadequate. At the same time, infants may not have access to DHM to supplement the low rates of MOM. This occurs even as HMBANA has grown 12% over the past year, with 6.5 million ounces of DHM distributed. Although resource-rich, less than 50% of NICUs in the US currently have access to DHM.

Access to DHM in LMICs, where the need for DHM can be argued to be the greatest, remains much lower than in HICs and thus is even more inequitable. The imbalance in the provision of safe, sustainable and assured supplies of DHM in all settings should be addressed.

Guidance would ideally address HMBs in the context of an optimal feeding systems framework – providing the practical guidance to maintain the standards by which HMBs should operate, while acknowledging that improving the supply of MOM should be the priority.

The commercialization of human milk and the subsequent potential for exploitation of families is of concern. Remuneration of the providers of milk to for-profit companies together with the provision of non-financial incentives require scrutiny, as does the provision of consent throughout the milk banking process.

Integration of Milk Banks into Health Systems

A systematic approach to human milk banking, where milk banks are integrated into larger health systems, is more sustainable and beneficial, but not common. This also has implications for the coverage of HMB services by health insurance. Additional costing data is needed – especially for an integrated system with breastfeeding, which creates a barrier to making a clear economic case for the return on investment in HMBs to the government at the national level. This may change if further studies were carried out including the long-term benefits of improved breastfeeding results.

Cost Effectiveness of DHM versus Formula

A randomised controlled trial (RCT) in Pediatrics (Trang et al., 2018) on the cost effectiveness of supplemental DHM versus formula for very low birth weight infants (a complete cost analysis of 400 babies randomised to DHM or preterm formula, with healthcare costs followed up and tallied for 18 months on) showed that although DHM was not cost saving, it also did not cost more than formula. The reason for this is that in developed countries, the single biggest driver of hospital costs is the number of days the baby spends in the hospital. In many neonatal units, babies on DHM are admitted for a few days longer, while waiting to achieve a target weight. These extra stay costs are weighed against the extra care costs resulting from the adverse clinical outcomes associated with formula use. That DHM is cost neutral when compared to formula could be viewed positively, given that DHM is nearer the norm for feeding babies compared to formula, which undermines breastfeeding. Other studies (Buckle & Taylor, 2017; Johnson et al., 2014; Mahon et al., 2016) have shown that DHM versus formula is cost saving.

Other studies have shown that although the rates of NEC are decreased, the cost savings from decreased NEC rates are offset by the costs of DHM, so there are no overall economic savings. With

MOM, there are further benefits, such as decreased rates of sepsis, so there is more robust economic data on the advantages of MOM that has not been shown with DHM.

Health Technology Assessments conducted within different country and health system contexts would help to shed more light on the overall and relative cost effectiveness of the contribution of milk banks and the availability of DHM.

Lactation Support

DHM should primarily be used as a bridge to full MOM and exclusive breastfeeding, and be recognised as an integral part of breastfeeding protection, promotion and support. Equally, all should be aware of the potential for DHM to be overused and MOM use be undermined by its availability. At the initiation of an HMB, there is an emphasis on conversations with parents around MOM as optimal nutrition and DHM as a short-term supplement. There have been examples when overall lactation rates initially improve on the unit but once the use of DHM becomes more established, there may be less of an emphasis on MOM, with correspondingly less support and volume. The major challenges are for all healthcare professionals involved in the feeding of newborns to be aware of the need for constant, ongoing and optimal lactation and breastfeeding support for new families, and to ensure the availability of DHM is integrated into and not an obstacle to BF support services (including the BFHI and the avoidance of inappropriate marketing).

It is important to be clear on the need for DHM, and the direction of any standards for HMBs. There is acknowledgement of the need to exercise caution with HMBs, so that DHM does not misleadingly usurp optimal feeding with MOM. At the same time, there is a need for coordinated, optimal lactation support to ensure every mother is supported to build an optimal milk supply.

Legitimising DHM with WHO standards

The publication of WHO standards will encourage countries to focus on the establishment of HMBs to make DHM available by legitimising its use. It is important to be clear on how countries should distribute their efforts between MOM and DHM. It would be helpful for the WHO to establish what the appropriate use of DHM is in the context of ideal infant feeding, including its limitations. Simultaneous guidance is needed regarding operational safety and clinical use.

Division into Working Groups

Based on the previous discussion, the group broadly agreed on the following:

i. Ethical issues associated with DHM should be at the forefront of any discussion.
ii. Milk banks should be situated within the health system, ideally within the framework of optimal newborn nutrition, with DHM used as a bridge until the use of MOM can be facilitated.
iii. It may be beneficial to place milk banks strategically under the MPHO framework.
iv. There needs to be further consideration of how DHM should be best used, what constitutes appropriate use and overuse, to whom it should be delivered, and for how long.
v. There is a huge lack of data, especially relating to issues of quality and safety, and lack of feeding and lactation support data globally, to support the need for DHM.
vi. Definitions of key terms used in milk banking are not unified, including the term 'DHM' itself.
vii. It is important that process management and policies are instituted at the national levels, with safety aspects built longitudinally into the process.
viii. Minimum standards of safety to ensure a quality product are needed, while being adaptable enough for globally diverse settings (resources, cultures).
ix. Further guidance is needed on how best to regulate HMBs.

Working groups were thus formed to explore the following:

i. Integration into Systems
ii. Strategy and Policy
iii. Quality and Safety

Each group was tasked to discuss the issues, challenges, research gaps, potential minimum standards, and potential global guidance or tools needed pertaining to the above topics. The groups were asked to pay special attention to the ethical issues relevant to the topic of discussion.

Presentations from Small Technical Working Groups

Working Group 1: Integration into Systems

Issues and Challenges

Building an HMB should tie into efforts to increase human milk feeding and breastfeeding rates, rather than be a standalone goal, with shared metrics of success being MOM feeding rather than, or in tandem with, volumes of DHM provision. A global issue at present is ensuring that governments have the ability to support sustainable, integrated milk banks, which involves financial ability as well as evidence-based interventions to ensure infants can receive MOM whenever possible. In addition to the health benefits for an infant, the presence of high human milk and breastfeeding rates will provide the DHM necessary to grow and sustain a milk bank.

Governments should be aware of the threat of commercialisation and commodification of DHM, with studies undertaken to better understand how they impact on the non-profit sector, including on volumes of human milk donation and attitudes of clinicians to the products being developed, and their practical and ethical implications.

Another challenge in integrating milk banks is the lack of healthcare provider knowledge on how to apply and utilise research-based interventions. There tends to be a reliance on PDHM when it is available. This is driven by the motivation to provide an exclusive human milk diet, with PDHM being the most convenient means of enabling this. Instead, there should be evidence-based lactation care, and the investment in equipment to facilitate infants receiving MOM. In certain contexts, this would involve providing access to refrigerators or freezers to store milk, and access to breast pumps for mothers. Funders tend to be willing to invest in HMBs (possibly because they are perceived to be a more impressive end product), and tend to be less willing to support mother's own lactation, which may overall be a less costly and more beneficial investment.

The team discussing integration into systems defined a vision statement as follows: To ensure all infants have equitable access to optimal nutrition.

It is crucial to define the terminology used in discussing optimal nutrition systems for infants. Only in recent years have researchers into breastfeeding or human milk started to define relevant concepts.

For example, there are differences between direct breastfeeding, MOM, PDHM and other milks. This needs to be stated clearly on any document or guidance pertaining to optimal nutrition.

MOM is the optimal way to feed infants whether healthy term or vulnerable hospitalised infants, while using DHM as a supplement for infants born very preterm has been shown to prevent NEC. However, controversary remains amongst some clinicians over whether DHM or formula would be better overall. Comprehensive clinical studies answering this question to the satisfaction of all have not yet been carried out.

Situations in which MOM is not available or not fully available are difficult to clearly define or fully outline. They comprise a range of categories which usually require investment in resources. Some barriers are modifiable e.g., through investment in technology and the application of current evidence-based knowledge. Others such as maternal death, disease and contraindication to the use of MOM are not. There should be recognition that it is not possible to completely alleviate situations where MOM is absent. Although challenging, this is also a concept that should be described in any document or guidance on human milk banking.

Currently, pasteurisation is generally assumed to be part of the standard processing of DHM. This assumption needs to be challenged. There is growing evidence of the disadvantages of pasteurisation in terms of the quality of the resultant human milk. A balance needs to be made between the safety and quality of DHM. In developed countries, there tends to be sufficient access to milk fortifiers to overcome some of these quality issues. The same standard of fortification may be complex to achieve in LMICs. It would be ideal to look for solutions that would allow the achievement of high levels of safety without DHM going through pasteurisation. Specialised screening of unpasteurised DHM is one way of maintaining an optimal nutritional profile while also maintaining safety. If PDHM is used, the concept of 'optimal pasteurisation' needs to be clearly defined. Variability in the process of pasteurisation affects the quality of DHM. This may be impacted by advances or access to improved technologies. This also affects the interpretation of studies relating to PDHM. The process of pasteurisation cannot be assumed to be equivalent, both between studies and in comparison to technology in use today.

The term vulnerable is another term that requires clarification. 'Vulnerable' should be broadly interpreted. Although the evidence for PDHM is mainly in relation to the prevention of NEC in preterm and low birth weight (LBW) infants, there are other vulnerable infant populations separated from their

mothers. These infants are not preterm, and their mothers may not be getting good evidence-based breastfeeding support and care. This includes infants undergoing surgery, infants with cardiac defects, infants with HIV positive mothers, and infants who are orphaned. There are research gaps in the use of PDHM in these vulnerable infants. Very low birth weight (VLBW) infants are also more likely to be in a NICU, and more likely to be separated from their mothers. Both infants and their mothers tend to be vulnerable in this population. Vulnerable mothers also have risks to their lactation and breastfeeding, and special attention should also be paid to their care to ensure adequate milk volumes.

As the evidence of the benefits of PDHM is most clearly established for decreasing NEC in VLBW infants, PDHM should be prioritised for use in VLBW infants in the absence of MOM. However, even in the absence of current published research, there is potential for the use of PDHM in other vulnerable populations, to facilitate an exclusively human milk diet and to avoid supplementation with formula.

Minimum Standards

As discussed in the working groups:

i. The focus of HMBs should be on the different needs of all vulnerable and sick infants, not just preterm infants.
ii. HMBs may be organised within a healthcare system, rather than be freestanding within a community.
iii. Regulation and quality assurance measures should be in place (these measures are as yet undefined), backed up by appropriate guidelines.
iv. There should be context-dependent considerations of the ethical issues relating to different standards of care.
v. As a prerequisite to initiating and maintaining a milk bank, high quality, evidence-based lactation care should be in place. Suggested human milk metrics to gauge this include the following:
    a. Values should be established of how many mothers of both term and vulnerable infants should achieve early breastfeeding or milk expression.
    b. Values should be established of how many sick and vulnerable infants should receive MOM for the first 28 days (this relates to evidence of positive health outcomes from exposure to MOM within this timeframe).

c. Demonstrate an ability to provide evidence-based lactation care to support the provision of MOM.
d. Up-to-date and evidence-based pre-service education for all healthcare providers, including a knowledge assessment.

vi. Milk banks should observe the legal considerations of their state and country.

Research Gaps

It is necessary to start collecting evidence for outcomes of interest other than the use of PDHM in preventing NEC. Anecdotally, PDHM is believed to prevent sepsis in neonates, but there is little evidence to support this practice at present. RCTs in high income countries have not shown a significant effect in sepsis reduction with PDHM, possibly because they have low baseline sepsis rates compared to lower income locations. It is possible that PDHM may be shown to decrease the risk and/or severity of sepsis in areas where the incidence of sepsis among neonates is higher, as it is in low- and middle-income countries. However, there is currently insufficient research to support PDHM use to significantly reduce sepsis in these settings. The cost-effectiveness of PDHM in LMIC settings is also under-researched. There is presently also no evidence on the use of PDHM on preventing NEC outside the NICU setting, e.g., in a paediatric cardiology ward.

The role of DHM in evidence-based optimal nutritional care is currently lacking among vulnerable infants who are not preterm or of low birthweight. Other research gaps include the role of PDHM in maintaining infant microbiota, and the long-term health outcomes of PDHM use beyond the NICU setting.

There are milk banks which have self-reported that term babies and otherwise well babies who are not volume restricted thrive on PDHM, but this has yet to be formally verified. The role of raw DHM in well infants, the population in which it is most likely to be safely tolerated, also needs to be further evaluated.

Implementation research on effectively setting up milk banks and on the measurement of standardised indicators is currently limited. In terms of infant parameters as an outcome, care should be taken to measure more than conventional growth standards – an infant may have a micronutrient deficiency, but still appear to grow well, despite for example suboptimal neurodevelopment.

The long-term outcomes of introducing PDHM into a health system, and its impact on lactation and feeding rates in the long-term, are unclear and need to be further studied, as does its availability on maternal outcomes including on mental health. There is evidence that introducing PDHM increases breastfeeding rates and human milk feeding in the short term. However, there are suspicions of a 'PDHM-creep', whereby PDHM eventually undermines optimal lactation and breastfeeding support if it is easier and more convenient for institutions to access and use PDHM than it is to support MOM.

Use Cases and Appropriateness

Given the current evidence, and as previously stated, it is clear that PDHM should be used in the absence of MOM for VLBW infants to decrease the incidence of NEC. PDHM is also used around the world for infants other than VLBW, but the relative absence of current research supporting this is acknowledged. The use of PDHM in less vulnerable infant populations may be warranted to promote an exclusively human milk diet and avoid formula supplementation, again acknowledging the absence of current research supporting this.

Although the research is lacking, it is of note that recommendations exist for exclusive breastfeeding, acknowledging the benefits of breastfeeding without systematic research evaluating its effects in all infant groups of specified weights, ages and medical conditions. It would be prudent to ask how far the burden of proof should be taken. DHM is often classed as an alternative to MOM which is not the case; it should be most fairly compared to other available supplements. Currently, the alternative is almost always only formula milk. DHM, especially when pasteurised, raises some open questions, and remains different from breastfeeding and MOM, but its use may still be appropriate even if this has not yet been clearly proven.

Additional Suggestions to Global Guidance

The primary goal of any optimal infant nutrition programme is preserving the mother's lactation and ensuring her milk supply, so that the mother-infant dyad can go on to breastfeed in the long run.

It is important to separate well mother-infant dyads from sick or vulnerable mother-infant dyads and a combination, sick mothers and well infants. However, it is important not to presume mothers and babies that are well are breastfeeding healthily – this should also be recognised, and the required support provided.

For mothers and infants at risk, the following is recommended if feasible:

1. Express milk early (within one hour of delivery), and pump often (8 or more times in 24 hours)
2. Have early and frequent skin-to-skin contact
3. Ensure the mother has come to volume effectively within the first 14 days (this predicts their ability to breastfeed in the longer term), and
4. Ensure sick and vulnerable infants have access to MOM during at least the first 28 days of life.

To examine optimal infant nutrition beyond the hospital stay, breastfeeding rates (stratified into the categories 'exclusive breastfeeding' and 'any breastfeeding') could be monitored for a defined period – for example, six months post-hospitalisation.

The following SWOT analysis may be useful for governments and departments of health in their evaluation of DHM:

Table 2 SWOT Analysis

Strengths	• Next best thing after MOM for VLBW infants at risk of NEC • Physiological benefits • Reduced risk of NEC • Opportunities for donors to 'do good' • Engages with new actors in neonatal care, promotes cross-communication between disciplines • Consistent with SDGs 1, 2, 3, 5 and 10
Weaknesses	• Depends on milk bank infrastructure/readiness • Lack of lactation specialists • Lack of data on DHM compared to alternatives (infant formula) • Lack of understanding of the place of DHM in optimal infant nutrition • Indications unclear • Requirement for fortification of preterm infants if longer term use • May have cultural and religious barriers
Opportunities	• Improve human milk feeding overall, with an aim to increase breastfeeding rate to a specified percentage • Strengthen breastfeeding and availability of MOM • Strengthen Early Child Development agenda

	• Advocacy for vulnerable infants • Improve human milk donation • Culture of priority setting • Research, especially cost-effectiveness and positive effects in different contexts (e.g., LMIC vs. HIC) • Improve holistic newborn care • Generate standards • Ethical discussions • International collaboration, both as a global HMB alliance and in developing research • Targets for improvement
Threats	• Resistance and ignorance from healthcare workers and physicians • Sustainability of milk banks • Cost • Donor recruitment • Donor exploitation • Lack of support to mothers • Lobbying from for-profit infant nutritional companies / Conflicts with commercial interests • Overuse of DHM • Equipoise contested to answer research gaps • Profit • Unintended harms e.g., PDHM becomes the default feed • Unclear terminology • Reluctance to invest in breast pumps • Safety and quality issues

Working Group 2: Strategy and Policy

The core issues when discussing strategic and policy issues include regulation, addressing gaps in data, advocacy, the appropriateness of human milk banking for that context, operational models, governance, financial issues and sustainability, and commercialisation and cross programme integrations such as newborn and nutrition.

Regulation

Regulatory issues pose a huge challenge to countries. These include the appropriate classification of human milk within specific health systems which vary greatly around the world, the complexities of regulating informal milk sharing, and policies that address the import and export of human milk.

As a minimum standard, regulatory bodies should be responsible for ensuring the safety and quality of DHM in all countries that practice human milk banking, and should promote safe breastfeeding practices. They should determine how human milk should be classified, and be aware of and regulate all aspects along the milk banking pathway, including the collection, storage, processing and distribution of DHM. They should also regulate the for-profit sale, purchase, import and export of human milk.

There are many ways regulatory bodies could fulfil these responsibilities. As an initial step, they could require all HMBs to be registered with them, so that the regulatory authorities have an overview of where they are located and how they can be contacted. In considering how human milk should be classified, regulatory bodies should take into account the purpose of such a classification and the accompanying regulations of various classification systems.

Other potential roles of a regulatory body include defining context-specific prerequisites for establishing HMBs, specifying the criteria for defining donors and recipients, determining appropriate data usage and protection (keeping in mind the need to maintain confidentiality but also the need to ensure robust tracking and tracing systems), determining the rules of financial engagement (for example, stating whether for-profit or formula companies are allowed to contribute to the financial operations of HMBs), and creating auditing and global accreditation systems for monitoring and control purposes. They should also determine how these regulations are enforced, and the consequences of violating them, including whether such infringements would constitute a civil or criminal offence.

Another consideration includes future developments in technology, resulting in the use of human milk and its components for other purposes and its corresponding ethical issues. One such use is the biobanking of human milk for its stem cells, which a donating mother may request that an HMB preserve for future therapeutic use.

Global guidance in terms of regulation could present the benefits and disadvantages of the different possible systems, outlining their principles and issues for consideration, with illustrations through case studies. Countries should be called on to develop their own context-dependent regulatory systems.
NB: In 2022, the European Commission adopted a proposal for a regulation on standards of quality and safety for substances of human origin intended for human application. The substances included in the standards will now include donor human milk. This proposed regulation concludes the revision of the legal framework for blood, tissues and cells, which did not formerly include human milk. See Addendum (page 86) for link to further information.

Addressing Data Gaps

Data gaps in human milk banking here refers broadly to the lack of coordinated data collection and reporting. It is not clear how many milk banks are in existence, whether they are community or hospital based, and the quality of their operations. Human milk banking data on processes, systems, distribution and usage should be tracked and available. HMB operational data should be linked to recipient outcome data. There is also a lack of costing data, especially with regard to self-standing and integrated milk banks and their long-term outcomes. Human milk banking data should be aligned and collected in a comparable manner, and there should be a system to support this.

There should also be relevant data on the target population that HMBs are meant to serve. This would include neonatal feeding and lactation support indicators, to give an accurate picture of whether babies require DHM, or whether systems supporting MOM need to be strengthened, or both.

Doing a randomised control trial in human milk banking would be extremely difficult but collecting implementational and operational data may be a practical strategy to build a solid research database. Prior to any change in operations, relevant data could be collected, and at a defined time point post-implementation, data collected and reviewed again. This would guide quality assurance. Implementational data is already being collected in neonatal units in Iran for example, which spent six months collecting data prior to initiating its first milk bank, with post-implementation data collected six months after implementation. This helps to evaluate how new actions mediate change and enables an analysis of its harms and benefits. As clinical units are expected to be doing such data collection as part of their quality assurance processes, this should cause minimal disruption to standard operating processes and funding. An additional challenge with HMB data has been the ability to link data to outcomes from clinical use. Although capturing comprehensive data would be a long-term goal, it may be useful to start with collecting basic information – such as feeding practices, lactation support,

breastfeeding rates at discharge, how DHM is being used and for how long – to initiate and guide the subsequent research agenda. Minimum requirements of HMB data collection and reporting should be established and shareable, including the standardisation of data collection for feeding preterm and sick infants.

Global guidance could call for the identification of gaps in newborn nutrition indicators, as well as HMB reporting gaps and the development of a reporting mechanism. The establishment of a global alliance of milk banks and associations would be able to have oversight and provide overarching guidance. Guidance would also be helpful to improve the indicators used to track feeding and lactation support for vulnerable infants.

Advocacy

In practice, established health professionals, including those specialised in infant nutrition, are often unaware or misinformed about DHM as an intervention. They are often also unaware of how to access DHM. This results in its misuse, with infants who need DHM potentially not receiving appropriate care. Guidance that places issues of access to DHM within the framework of human rights may improve advocacy for HMBs. To ensure the political commitment of governmental organisations, the guidance could suggest that member states should have a defined policy and strategy on improving neonatal health by contributing to optimal nutrition, specifying that this includes the availability and use of DHM.

Appropriateness and Demand

The inappropriate use of DHM and the inappropriate establishment of HMBs may result in the unnecessary diversion into a milk bank of resources that may be better invested elsewhere to improve outcomes. Key elements that need to be in place prior to the establishment of a milk bank include supportive breastfeeding policies, data demonstrating that strategies to acquire MOM are in place in NICUs, safety and quality regulations, documentation of the need for HMBs before opening an HMB, and an audit system in place to check appropriate use once one is established. Inappropriate use of DHM increases the potential for exploitation, undermines breastfeeding and the provision of MOM, and damages the reputation of milk banking.

Countries should have clear policies on the appropriate use of DHM, and state the prerequisites for the establishment of an HMB. This should come under the watch of a national regulatory body.

Operational Models

Different operational models may have different strengths and efficiencies. In North America, multiple milk banks with different operational models co-exist, and often compete. It can be challenging to coordinate such milk banks and their competing interests, and competition for regional access may impact on efficiency. Countries may optimise efficiency by integrating milk banks into the larger healthcare system and linking them to breastfeeding and lactation support. Countries may also consider determining estimates of the expected volume requirements needed from milk banks. This would be based on specific use cases. Once the burden is identified, and the required volumes of DHM estimated , efficient operational models can be developed to meet that need.

To establish the most appropriate model for their context, countries would benefit from case studies and a consideration of the benefits and disadvantages of present operational models.

Commercialisation

Commercialisation is a major issue. On the one hand, commercialisation could be said to have benefited milk banking by attracting funding to drive innovation and research, although conflicts of interest are often cited. On the other hand, it can be exploitative. Commercial milk banks tend to promote their products as safer alternatives to those from non-profit milk banks, even though their processes are largely not transparent, and the quality of their products is often unknown. This also undermines public trust and confidence in non-profit milk banking models.

A WHO Position Statement is urgently needed to outline the issues surrounding the commercialisation of HMBs, the position of DHM within the International Code of Marketing of Breastmilk Substitutes (the Code), and the protections that countries should consider.

There are specific issues in the marketing of DHM that mimic or are analogous to the inappropriate marketing of human milk substitutes. Based on experience, the Code, as practiced within countries, is a national adaptation of the International Code of Marketing of Breastmilk Substitutes; this adaptation is then adopted into law. Although DHM is not a mother's milk substitute, the provisions of the Code should still apply to it if it is used to displace MOM. This introduces confusion at the layer of government regulators, who may not fully understand the classification of this product. From a legal perspective, commercial HMB entities would currently be able to advertise via mass media and make

health claims about their product, since they are not technically covered by the Code, although this would be ethically questionable. Recommendations related to the Code need to be made clear, including practices that should be prohibited or regulated in some manner.

Governance

There is no consensus on what actions leadership in human milk banking should provide. The range of responsibilities potentially includes advocacy work, engaging in policy development and implementation, monitoring of HMBs including technical reviews of standard operating procedures and audits, and mentoring for both existing and newer milk banks.

Global and national oversight is lacking in human milk banking. A leadership body constituted of representatives from various technical backgrounds relating to human milk banking is likely to be beneficial. It is not unusual for the directorate of milk banking institutions to have a background in nutrition. A collaborative effort involving experts in child and newborn health, and experts in biosafety and global newborn and nutrition policies, would be appropriate.

There are many commonalities between milk banking guidelines, although there are some differences which need to be resolved if they do not adhere to core minimum standards. The European Milk Bank Association has created regional guidance by reviewing the guidelines and recommendations from all its members. A recommendation was passed where consensus existed. Where there was a lack of consensus, evidence was sourced to support a recommendation. Where there was neither consensus nor support, an agreement was made based on expert opinion. The EMBA guidance and its review processes might be a good starting point for including other global realities into a unified guidance document. Areas of important technical gaps could then be reviewed by an international working group, which could later reconvene to review and harmonise practices.

The milk banking community has identified the need for a global alliance of milk banks, bringing together different sectors of healthcare on both the national and international levels, and addressing the many issues raised in milk banking as a whole. Guidance has been requested on how best to establish such a global entity.

Financing and Sustainability

Covering the cost of DHM for recipients is a major challenge, especially in countries without universal health coverage. The financing of DHM must be considered when deciding on the most appropriate operational model for a milk bank. Insurance companies need to have sufficient data to merit coverage of DHM where relevant. At present, there are inadequate routine data systems that enable understanding or recognition of the cost burden globally. Government authorities also need evidence to support the use of DHM in the local setting – this is likely to include its predicted impact and a health technology assessment. If funded publicly, it may be wise to consider the right of the child to human milk, as included under the human rights framework. It would then be the responsibility of a democratic government to ensure that all children have access to human milk.
Governments may distinguish the different capacities of their citizens to afford DHM. In India, citizens identified to be living below the poverty line are allowed to access DHM with no out-of-pocket expense, as this is covered by the government. Another alternative is a cost-recovery model, where the public system may contract services for a specified provision of DHM based on a calculated cost estimate. Funding models would be different for different countries, depending on their public and private health provisions, and this should be part of the guidance for countries trying to establish a milk bank.

Costs can be significant; ongoing operating costs can be embedded in current systems, if designed appropriately. If the operations of HMBs are publicly supported, their financing can be linked to the data collection needs of the health ministry. A precedent for similar financing models has been set in the field of renal dialysis. In countries like Thailand that have implemented universal coverage for renal dialysis, it is mandatory that each dialysis unit fills out the data required by the respective registry before the unit is reimbursed.

Documenting the need for HMBs in a country should be a foundational activity prior to initiation. Documentation of such a need would encourage funding and identify other related areas in neonatal care that require further support, and provide data that would be useful for furthering neonatal care at both a national and global level. Nevertheless, the lack of agreement on which infants should receive DHM and for how long is somewhat complex, especially in terms of assessing operational size which in turn drives costs.

Working Group 3: Quality and Safety

There are numerous challenges in determining quality and safety standards for human milk banking and DHM. Much of this is because of the lack of evidence to guide this process. Planned innovations

and new technologies, as described previously, will necessitate these being readdressed as they become available.

Practices vary considerably between milk banks. Many of the methods and equipment employed in current practice are not validated for use in human milk. Although researchers involved in human milk are aware of these gaps, funding to fill these research gaps is often deprioritised, and issues relating to HMBs often do not fit into the available funding strategies.

The intent of these processes is to optimise the final product. As yet, there is no clear idea or definition of what optimal means for DHM, in part because it has not been clearly characterised as a product. In an ideal situation, the composition of raw human milk and the optimised product from an HMB should be identical. However, if the quality of DHM was on a par with MOM, that would potentially make it even more difficult to ensure the DHM was being used appropriately, i.e., not in competition with MOM and in the context of optimal support for maternal lactation and breastfeeding. The fact that MOM is highly superior to PDHM drives the necessity to maximise MOM use. In practice, DHM is unlikely to ever match MOM for initiating and for early enteral feeds because donated colostrum is not generally available, and there would be ethical concerns over trying to increase donations of colostrum.

One limiting step in optimising DHM is the inability to reliably analyse DHM, and accurately and meaningfully characterise it. There are few specialised laboratories that can measure the macronutrient profile of DHM accurately. Equipment developed and intended for human milk analysis is widely used throughout Europe and further afield, but some milk banks employ commercially available technical equipment meant for use in the dairy industry. Ethical concerns are raised when low resource countries invest in high-cost equipment to analyse human milk when the results may have little or no positive bearing on the overall process or are of questionable benefit to the recipients.

Some milk banks are expected to, and do, provide information on protein, fat and energy content to help inform the choice and use of PDHM by neonatal clinicians and dietitians. This practice is a legacy of formula milk use, in which nutrient values can be clearly calculated and milk volumes ordered accordingly, and is largely in response to an expectation of some current health systems, despite the clinical significance of these numbers needing further evaluation. It also ignores the valuable non-nutritional components present in PDHM such as human milk oligosaccharides, immunoglobulins, growth hormones and other bioactive proteins. Globally, DHM is largely used as a therapeutic

intervention to save lives, and the differences in caloric values are less relevant than the immunological and other benefits which an intervention with DHM may provide.

If human milk could be accurately analysed, optimising its use would remain complex and not always possible. For example, the bioactivity of proteases in human milk depends on interactions with the infant gut. This then affects the bioavailability of peptides. What is measured in the milk may then not reflect what the infant is able to absorb. Understanding and interpreting which nutrients should be measured is also complex – for example, DHM may have normal levels of measurable fat content, but its digestion and absorption may be affected by the reduction of the heat labile lipase in the same sample. Standard fortification of human milk in terms of calories and protein may be ignoring other valuable components of DHM, namely its bioactive components. In some scenarios, milk is rejected as a result of not meeting defined caloric or protein requirements of preterm infants for example, despite it being adequate for other populations of infants, or for those who only require short-term supplementation with DHM, and for whom nutrition is not the primary benefit of this supplementation.

Although it is not possible to fully define optimal, it is the responsibility of the milk bank production team to assess the systems that are already in place, understand the profile of the product being delivered, and evaluate in small increments whether interventions increase or decrease its nutritional profile when compared with other methods, with a particular focus on retaining a higher content of potential biological activity. It is important to note that the donor profile differs across the world, which is a major factor affecting milk quality. The nutrient and non-nutrient profile of milk donated by mothers with very young (days or a few weeks) and possibly low gestation infants will differ markedly from that of donors at home feeding babies who are several months of age or older. The constituents of human milk will also vary on a day-to-day basis. Milk will not be uniform despite similar practices among milk banks. Understanding current practices would be a starting point in setting the initial standards which milk practices may later improve upon. Understanding and optimising donor recruitment should also be part of this process.

Considering the current inability to define or achieve optimal quality DHM, it could be defined as DHM with the highest retention of as many as possible beneficial properties, and with the lowest pathogenic activity. DHM might need to be reconceptualised from being a singular product to becoming a range of human milk products sourced and processed in different ways to meet the needs of defined end-

users. Optimising the product would then be about making it effective for those purposes, rather than making it perfect.

Much of the research into human milk tends not to take into consideration the larger health system. There should be an emphasis on situating HMBs within the healthcare system, and for them or their outreach to include high-quality lactation support and care. In assisting mothers, some of the quality issues around DHM will be addressed. For most babies, the use of DHM is intended as a bridge until they can fully access MOM. Using DHM in this manner aims to facilitate MOM and reduce the time that infants require DHM. At the same time, by facilitating MOM, more mothers will be eligible to also donate milk – thus enabling an increase in the recruiting and matching of donor mothers to recipient infants (for example donor mothers of preterm infants with preterm recipients, or human milk oligosaccharide profiling), to provide DHM that would be most similar or complementary to the mother's milk if available, and most beneficial to the recipient infant's needs. At the same time, while trying to optimise DHM, there needs to be awareness of children receiving suboptimal MOM, for example when their mothers are severely malnourished, and providing them with commensurate support. Although concern has been expressed regarding the use of DHM long-term in term infants, studies have shown that healthy term babies will upregulate their milk intake based on their nutrient intake.

The quality and safety of DHM should always be taken into consideration. For example, to prevent the transmission of pathogens, milk banks should consider how to screen donors and/or milk samples, how to set up internal processes to prevent microbial contamination during handling, and whether pasteurisation is always necessary, as pasteurisation will have a negative effect on the natural microbiome of human milk.

Another step in ensuring a safe product of acceptable quality would be process mapping. This would entail a global review of current practices, mapping both the differences and common points, which could also be marked as points of quality control. The output of this process would be a form of guidance. For example, it may state that a test for pathogenic microorganisms would need be done at a certain point, mention how this should be done and what is being tested for, state the maximum and minimum acceptable limits of this test with an explanation on how this was determined, and mention what might be further looked at. This would enable and examine the use of current practice to determine an initial set of guidelines, while awaiting the results of more comprehensive and targeted research.

Within current practices, microbial testing is an issue that needs to be highlighted. Although it is one of the primary issues linked to safety, there is a marked variation in practice, with different methods and sample types being used. An analysis and validation of current practices would be useful, with guidance on the safe range of practice, taking into account the variability in access to tests to identify bacteria to genus and/or species, especially in LMICs.

Global guidance should consider a call for an alternative means of processing human milk that is specific to human milk, retaining its valued bioactive and microbial components while providing an acceptable level of safety from pathogens.

Another area of immediate guidance would be in suggesting that new milk banks are systematic in their development, with an analysis of different processes that milk banks can apply. This would be a means of developing locally relevant quality assurance plans. For example, the Hazard Analysis Critical Control Point process is included by India in their milk banking guidelines (Child Health Division Ministry of Health and Family Welfare Government of India, 2017). This would help to address foundational quality and safety issues in a contextually relevant manner. Other useful tools include the development of quality assurance standards that milk banks could use for audit purposes.

It is important to be aware of the baseline uniqueness of human milk and the variations post-processing, resulting in different types of end products. Quality in DHM is not just about having the best available product. It is also about having sufficient supplies of the most appropriate product for a particular infant, at a given time and made available using appropriate guidelines, in the same way that the relevant aspects of the use of other biological therapeutic products are considered.

Conclusion and Recommendations for Further Action

There was a clear consensus throughout all the discussions that all infants should have access to optimal nutrition, and that making available MOM as an optimal nutrition source should be supported as much as possible. DHM is the next best alternative but, due to limited research, the composition of optimal DHM and its necessary properties are difficult to define. This results in variations in its composition with regard to its nutrient and non-nutrient properties, and these will have clinical implications.

The aims of this meeting were to define knowledge gaps with regard to human milk banking, to

determine the need for global guidelines and the framework of such guidelines, and to provide recommendations on steps that need to be taken at the international level.

An array of knowledge gaps impeding the formulation of best practices with regard to DHM banking were identified. These include the lack of evidence regarding optimal processes such as pasteurisation and fortification techniques, the lack of medical evidence regarding which specific populations may benefit from DHM (apart from neonates at risk of NEC or feeding intolerance), and difficulties in measuring outcomes. Various practical challenges with the establishment of HMBs in a range of settings were also identified. These included the use of DHM instead of MOM due to convenience of access, and the possible exploitation of human milk providers in profit-driven human milk processing operations. The availability of training opportunities and competency assessment should be highlighted as a means to avoid the misuse of DHM and to ensure safe practices within milk banking operations. For optimal newborn health, guidance is needed primarily to ensure safe and optimal quality DHM is available to meet the needs of preterm, low-birthweight infants without access to MOM.

Given the expansion of and interest in human milk banking, particularly in LMICs, the overall conclusion was that evidence-based guidance is urgently needed. Closing the research gaps will be an important next step driving the process of developing context driven recommendations, minimum standards, and guidance tools for the donation, use, storage and distribution of human milk.

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