International Expert Meeting on Donation and Use of Human Milk

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Draft Meeting Report

Drafted by Mirriam Tyebally Fang

Organizing team:

Stratos Chatzixiros
Consultant, Medical Products of Human Origin (MPHO)
World Health Organization

Laurence Grummer-Strawn
PhD, MPA, MA
Technical Officer, Department of Nutrition for Health and Development (NHD)
World Health Organization

Nikola Biller-Andorno
MD, PhD, MHBA
Director, Institute of Biomedical Ethics and History of Medicine, University of Zurich

Mirriam Tyebally Fang
M.B.B.S, M.R.C.S
Institute of Biomedical Ethics and History of Medicine, University of Zurich

Authors of Background Documents:

Technical Considerations on Human Milk Banking

Deborah O'Connor
RD, PhD
Professor and Interim Chair,
Department of Nutritional Sciences, University of Toronto

Sharon Unger
BSc, MD, FRCP(C)
Neonatologist and Professor, Sinai Health System

Global Overview and Status of Human Milk Banking

Cyril Engmann
MD, FAAP
Global Program Leader and Director, Maternal, Newborn, Child Health and Nutrition,
PATH

Kiersten Israel-Ballard
DrPH
Associate Director, Maternal, Newborn, Child Health and Nutrition Global Program
PATH

Kimberly Mansen,
MSPH, RDN
Program Officer, Maternal, Newborn, and Child Health and Nutrition Program
PATH

Overview of Operating National Tissue Banking Programs

Marisa R. Herson
General Secretary of the World Union of Tissue Banking Associations
Advisor expert, WHO Taskforce on Human Organ and Tissue Donation and Transplantation

Gillian Weaver
Co-founder, The Hearts Milk Bank
Former President of the European Milk Bank Association

List of Participants:

Akram Karami, BSc.
Breastfeeding Consultant, and Artist (Calligraphy)

Anne Grovslien
Breastfeeding Counsellor and Multi-cultural Health Co-ordinator

Antoni Gaya, MD PhD
Founder, Spanish Association of Human Milk Banks (AEBLH)
Co-Founder and Board Member, European Milk Bank Association
Board Member, Spanish Association of Tissue Banks

Ben Hartmann, PhD
Manager, PREM Milk Bank, King Edward Memorial Hospital, Subiaco, Western Australia
Expert advisor on safety, quality and ethical practice in human milk banking

Diane L. Spatz, PhD, RN-BC, FAAN
Professor of Perinatal Nursing & Helen Shearer Professor of Nutrition, University of Pennsylvania School of Nursing
Director, Lactation Program, Children's Hospital of Philadelphia (CHOP)
Clinical Coordinator, CHOP Mother's Milk Bank

Dragoslav Domanovic, MD, PhD
Senior Expert, Vigilance and Traceability of Tissues and Cells of Human Origin, European Centre for Disease Prevention and Control, Stockholm, Sweden

Estrella J. Olonan-Jusi, MD, MPM
Medical Specialist III, Department of Paediatrics, Dr. Jose Fabella Memorial Hospital
President, Human Milk Bank Association of the Philipines

Jim Gray, MRCP, FRCPath
Consultant Microbiologist, Birmingham Children's & Women's Hospitals, England
Expert Advisor, British National Formulary for Children

Lucy Culshaw, PhD
Senior Research Engagement Officer, Bliss – National charity for newborns, UK

Mohammad Bagher Hosseini, MD
Neonatologist and Associate Professor of Paediatrics and Clinical Director, Neonatal Intensive Care Unit, Alzahra Teaching Hospital of Tabriz, Tabriz University of Medical Sciences
Director, Breast Milk Bank of Tabriz University of Medical Sciences

Paul Andrew Zambrano, MD, MSc
Regional Technical Specialist (South East Asia), Alive & Thrive

Paula Meier, PhD, RN
Professor, Paediatrics and Nursing
Director, Neonatal Intensive Care Unit Lactation Services, Rush University Medical Center, Chicago
Former President, International Society for Research in Human Milk Banking
Member, Health Advisory Council, La Leche League

Penny Reimers, RN, RM, IBCLC
Founding member, Human Milk Banking Association of South Africa

Prasanth K. Subramanian
Senior Consultant, National Health Systems Resource Centre, National Health Mission, Ministry of Health and Family Welfare, Govt. of India

Robert Wahome
Medical Laboratory Scientist, Pumwani Maternity Hospital, Kenya

Shinya Ito, MD, FRCPC
Professor and Chief, Division of Clinical Pharmacology & Toxicology, Department of Paediatrics, Hospital for Sick Children , University of Toronto
Professor of Pharmacology/Toxicology, Medicine and Pharmaceutical Sciences, University of Toronto
Senior Scientist, Research Institute, Hospital for Sick Children

Valerie Lucyx, MBBCh, MSPH, PhD
Consultant, WHO Global Health Ethics Team

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***Executive Summary to be added once contents of meeting report confirmed**

Background

In July 2019, a group of international experts in fields relevant to human milk banking gathered at a meeting organized 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, which called into question whether a need for authoritative global guidance on human milk banking was a necessary next step.

Human milk is considered pivotal for optimal infant health. The World Health Organization and UNICEF prioritize donor human milk (DHM) as the prime alternative for low birthweight infants when a mother's own milk is unavailable, in settings where human milk banks are available or can be established. In practice, this would include neonatal intensive care unit (NICU) settings. Despite these recommendations, little guidance exists on the implementation, operation and regulation of human milk banks, and no further support been established for ensuring the safe use of donor human milk for infants who need it.

The aim of this meeting was to:

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

The term 'milk bank' as discussed in this meeting was specified to mean a facility where donor human milk is collected, processed, stored and subsequently distributed to meet the healthcare needs of preterm- and sick infants (to be distinguished from peer to peer milk sharing networks, or milk banks used for other purposes).

The choice of participants to the meeting ensured both regional representation (based on WHO classifications, with representation in the following regions: Africa, Americas, South East Asia, Europe, Eastern Mediterranean, and Western Pacific) and professional representation of various stakeholder and expert groups relating to human milk banking. The 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) , managers of milk banks, clinical researchers with a special interest in lactation and human milk, public health relating to nutrition and child development, infectious diseases (with a focus on medical products of human origin (MPHO)), microbiology, pharmacology with a focus on drug excretion into milk, blood safety, tissue banking, and patient-donor organization representatives.

Taking into consideration the varied backgrounds of participants, 3 background documents were commissioned by subject experts on the following, with aims as follows:

1. 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.

2. A review of national tissue banking programs (with a view to cross-applicability to human milk banking)

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

3. A scoping paper and literature review on the technical aspects of human milk banking

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

The documents were researched and made available to participants prior to the meeting proper, and were presented at the onset of the meeting to facilitate any necessary clarifications.

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

i. Content that was a clear case for guidance
ii. Content that should clearly not be regulated (for example, because it would harm the running of smaller milk banks, or because the content was irrelevant)
iii. Knowledge gaps, especially with regards to the practical challenges of milk banking and contested issues

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

We would like to present here the key findings from the research documents above and the discussions that followed.

Introduction

Breastfeeding is recognized as an essential part of newborn care. Where a mother's own milk (MOM) is not available, donor human milk exists as a safe alternative via milk banking. At the moment, although human milk banks (HMB) exists in over 60 countries, the vast majority of HMB's are situated in America, Brazil and Europe, with only a small number in low and middle-income countries. Most WHO member states have yet to establish national policies or programs that support the provision of donor human milk 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, and targets for maternal, infant and young child nutrition.

Donor human milk is considered a 'medical product of human origin' (MPHO) by the World Health Organization. An MPHO refers to biological material, derived wholly or in part from the human body and processed using human labour and technological intervention, intended for clinical application. For many diseases with no other available treatment, the use of MPHO's can be a vital intervention to prolong life, reduce morbidity, and improve quality of life. MPHO's fall under the category of 'universal coverage', in that everyone should have access to life-saving products. A distinct set of principles apply when it comes to the donation and management of MPHO's, as set forth in the Common Framework on Medical Products of Human Origin (2017)[1]. 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 risks to public health through appropriate donor selection, screening, and testing, processing the MPHO to prevent disease transmission, to ensure traceability in the event of a sentinel event, and to level inequalities in access to MPHO's.

The first principle in promoting the ethical practices in the donation and management of MPHO's states:

"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 programs that support the provision of donor human milk to infants who need them. The WHO is now engaged in the development of product-specific material based upon the Common Framework on Medical Products of Human Origin, with human milk banking identified as a high priority product.

Other principles of the Common Framework on Medical Products of Human Origin 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."

DHM is presently preferable to infant formula as an alternative to MOM. The availability of DHM and support for milk banks may siphon support from assisting mothers with establishing and maintaining their own milk production, with DHM being a more convenient and less time-consuming product compared to supporting breast-feeding mothers. Alternatively, a mother may want to feed her baby human milk, but may not want to breastfeed herself by way of preference, wishing to rely instead on DHM. In this way, DHM may start replacing MOM.

For the purposes of this meeting, we limited our scope to the establishment of human milk banks serving premature and vulnerable infants, but we also recognize that the clinical utility of human milk is not limited to infants, which is an issue which will need to be contended with. For example, the use of modified human alpha-lactalbumin (a protein found in human milk) is currently undergoing clinical trials in Sweden 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."

And

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."

The provision of financial incentives for DHM may encourage the coercion and exploitation of women from poor financial backgrounds, with women from low-income families making the majority of donations to support themselves and their families. It may further stigmatize donors, disincentivizing other women who wish to contribute to human milk banks. Financial incentives may also compel women to conceal personal practices and medical history that may jeopardize their donation of human milk, and hence their payout. 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.

At the same time, the actual cost to a family of providing DHM is different from that of other kinds of MPHO. A donation of blood, for example, takes about an hour every few months. A donation of human milk if done regularly over period of time, requires a commitment of pumping regularly throughout the day for the duration of that time period. The time spent pumping puts a significant burden on the donor woman, and the lack of reimbursement devalues her time and effort.

At the same time, allocation systems, especially when insurance does not cover the provision of DHM and families have to pay out of pocket for access to DHM, may preferentially favour infants from higher socio-economic status's, leading to inequity in terms of both the burden of donation and the advantage of benefiting from a donation.

At the present moment, there are no clear guidelines ensuring fairness in terms of how milk should be collected or distributed.

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, 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 the consumption of large amounts of energy and the mobilization of nutrients from maternal stores. There is also potential to harm their own babies if their milk is diverted from their babies towards donation (for example, to benefit from financial incentives).

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 of the donation and the cultural significance of the donation. Directed donations, where a lactating woman would like her donation to benefit a specific infant, may increase the overall donation pool, and allow existing donor milk to reach a larger population. These women may want to develop a relationship with the donor. For example, it is helpful for mothers who have lost their own infants see the impact of their donated milk on another mother-child dyad as part of their grieving process. Muslims also believe a kinship develops between the offspring of the milk donor and the recipient of the donor milk, and restricts marriage between the two. It is culturally important then that the identities of both children are disclosed.

Principle 9:

"In order to minimize 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."

Traceability is a particular concern and challenge in milk banking, as milk is pooled together, and feeds happen regularly over a potentially long period of time.

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. The BFHI states that in any facility with pre-term infants and other vulnerable newborns, 80% should be on human milk. This supply of human milk needs to be somehow established, and done so in a safe manner, especially when a mother is unable to provide her own milk. 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'. The triple billion target is aims to ensure 1 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. Guidance for donor human milk and human milk banking has been defined as a potential product, that has been proposed to countries as "Policies and standards for quality, safety, and guidance on the establishment, operation and regulation of human milk banks." Member countries have indicated interest in prioritizing guidance for human milk banking for the WHO to take further action.

Key points from presentation: Technical Considerations on Human Milk Banking

Donor human milk is defined as human breast milk in excess of an infant's current and future needs that is donated by a mother for use by an infant other than her own. A human milk bank refers to a service established to recruit breast milk donors, collect donated milk, and then screen, process, store and distribute the milk to meet infant's specific needs for optimal health. Human milk banks are often part of a hospital facility, or a related breast-feeding enterprise.

Human milk, unlike formula, is a widely complex fluid, and donor samples can vary widely in their composition. Although 50% of the energy from human milk comes from fat, the fat content in donor human milk may vary considerably from sample to sample. The most significant variable impacting the composition of milk is lactational stage, although even the composition of mature milk changes over time. In general, the majority of donor milk tends to be mature milk. Other factors 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 complete breast expression). To address the variability in nutrients, milk is pooled, usually from 3 – 4 mothers. Care is taken in the field of human milk not to alarm breast-feeding mothers about the nutrient-variability of their milk. However, with donor milk as a product (rather than a physiological fluid), there is a need to acknowledge the maternal factors affecting nutrient composition.

Another important consideration is the microbiome profile of donor human milk. While the natural microbiome is generally beneficial, approximately 25% of milk cultures culture positive for a known pathogen, which can be an issue when donor human milk is fed to vulnerable infants. Reducing pathogen count starts with donor selection. It is beneficial when interaction with donors is done by

trained staff, for example lactation consultants and diet technicians. In Canada, the initial screening interview establishes:

i. That the potential donor produces at least 5 litres of milk (this is in consideration of logistics costs)
ii. Donor and infant health
iii. Donor lifestyle and behaviours relevant to the safety of the donation

This is followed with the following procedures:

i. Informed consent
ii. Serology – using the established standards required for blood donation, with the addition of nucleic acid testing
iii. Obtaining approval from the donor's physician and the infant's paediatrician to proceed with the donation

The exclusion criteria follows that of the Human Milk Banking Association of North America (HMBANA) guidelines.

Guidance is also given over the phone on how to express milk to reduce the bacterial load, and to explain the logistics of transporting the expressed milk to the bank. A pre-culture of $< 5 \times 10^7$ CFU is the cut-off for donated milk to enter the pasteurization stream.

Informed consent also needs to be taken on behalf of the recipient infant. This informed consent should include information on both donor milk and formula milk.

Other significant quality control measures include: sufficient staff training, establishing protocols for equipment and maintenance, record-keeping, and audits both with regards to food-safety and as a donation facility.

Donor milk goes through at least two freeze-thaw cycles and approximately 5 container changes when processed. This further affects the fat composition of the milk. Freezing affects both nutrients and bioactive substances. Frozen fat globules tend to adhere to the sides of the containers, reducing the energy-content of the milk during container changes. Most milk banks process raw milk using Holder pasteurization, in which milk is held at 62.5°C for 30 minutes. In practice, depending on the rates of heating and cooling, donor milk may be held at high temperatures for longer than an hour. While there is good retention of some nutrient and bioactive substances, there are also substances that are drastically

reduced or eliminated, with live cells being most affected. The effect of Holder pasteurization on bile salt dependent lipase is of particular concern. Most fat contained in human milk is in triglyceride form. Fatty acids need to be separated from the glycerol backbone to be absorbed. The stark reduction of bile salt dependent lipase post-Holder pasteurization further diminishes the fat and energy content available to infants via donor human milk.

There is an on-going effort to develop alternative methods of processing donor human milk. The European Milk Banking 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. However, its feasibility has been questioned as it may not be sufficient to destroy all viruses. 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. Although promising, there are presently limitations such as the availability of equipment and the ability of milk banks to accommodate bulky equipment that present as barriers to their use. Using different methods, what we know now in terms of post-processing donor milk composition may change in a few years, requiring flexibility in thinking about the composition of human milk.

A Cochrane review published in 2018[2] evaluated the evidence comparing formula and donor breast milk for feeding preterm or low birth weight infants. Most 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. The use of unfortified supplemental donor human milk was seen to impact the growth of infants, with poor weight gains and reductions in length and head circumference. Few studies evaluated fortified donor human milk and the subsequent effectiveness of donor human milk, as that was not the general practice then, and little information was published on the long-term effects of donor breast milk. A further Cochrane review in 2016[3] evaluated multi-nutrient fortification of human milk on preterm infants. While there was no review comparing various fortification strategies for donor human milk with MOM, the studies looking at fortified human milk in general showed short term increases in weight, linear gains, and head circumference growth, even when accounting for birth weight and income levels. Importantly, no adverse effects were noted with the multi-nutrient fortifier use, including necrotizing enterocolitis (NEC), even though most fortifiers are bovine - based. The lack of evidence linking short term gains to long-term effects needs to be interpreted with caution: this may not necessarily reflect the futility of DHM on health parameters in the long run, but is more likely a consequence of the lack of studies on the subject, which are further limited in practice by ethical issues such as denying fortifiers to a group of infants to study its long-term effects, given that multi-nutrient fortifiers are the current standard of care.

The review was, however, clear that the use of supplemental DHM did prevent NEC, and that feeding tolerance was improved with DHM. An improved feeding tolerance meant that infants could be removed from parenteral nutrition and be fed enterally instead.

A randomized clinical trial [4] comparing the effect of supplemental donor human milk compared with preterm formula in very low birth weight infants 18 months later showed an overall decline in weight and length for age in both groups of infants, with no statistically significant difference between the groups. This suggests that growth and likely nutritional intake were suboptimal in both groups.

Donor human milk for healthy term infants may be a source of revenue for milk banks and hospitals under financial pressure. While acknowledging the benefits of mother's own milk and the presence of bioactive components in human milk in general, little evidence exists on the impact of donor human milk on healthy term infants.

It is uncertain whether DHM, as processed today, can be considered a complete source of nutrition. The nutrient composition post-processing can be altered dramatically from the daily recommended intake for infants. Folate, for example, is an essential nutrient required for cell division and growth and is especially important in the neonatal period where early rapid growth occurs. An adequate intake of folate is estimated to be 65 micrograms per day, and the average folate content of human milk is estimated to be 85 mcg/l. Assuming a neonate has an intake of 700 ml/day of donor human milk, processing that milk through freezer-storage (up to 50% reduction of folate if stored in a freezer for 3 months at - 20 degrees Celsius) and Holder pasteurization (up to 25% reduction of folate), leaves us with an intake of 26.5 mcg of folate per day. It is questionable whether this is enough to meet the nutrition requirements of a healthy pre-term infant fed exclusively on donor human milk for 6 months, and exemplifies the importance of evidence in determining best practices. If donor milk is given to healthy term infants, it should be supplemented with a multi-vitamin.

The literature elucidating motivations behind donating human milk is limited. In some countries, it is against the constitution to pay for biological materials, including human milk. This is the case in Canada, for example. Putting aside financial reasons then, other motivations for donating milk include: feelings of altruism, putting to good use excess human milk produced, and access to breast-feeding support through milk donations. Anecdotally, the opportunity for bereaved mothers of pre-term infants to donate their milk is also said to help with the grieving process. These motivations remain under-researched.

On the ground, allocation of DHM is a more practical issue that tends to be supply-dependent. In Toronto, when supply is considered limited, the distribution of donor human milk follows the evidence, and is provided especially when babies are at risk of NEC. The NEC protective period is usually about 34 weeks post-conception. However, as the supply is often more than sufficient to meet needs, the use of donor human milk tends to be allowed up till 36 weeks post-conception. As a result, mothers may not understand their own supply before being discharged from hospital care. In Toronto, donor human milk is not provided to healthy term infants although there is a lot of pressure to do so.

The provision of human milk is not financially reimbursed in Canada, but this is not necessarily the practice world-wide. For example, although organizations such as HMBANA do not pay mothers for donations of human milk, there are also 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 taken from both donors, who should understand how their donation is being used, and recipients of human milk. Clinicians and policy-makers need to remain vigilant of conflicts of interest with for-profit companies that may affect decision-making about the use of DHM. These companies may support faculties with research projects and conferences, support trials of their products in clinical units, and support support groups for parents of preterm infants.

Mother's own milk is acknowledged to be the optimal way to feed infants. This needs to be distinguished from donor human milk as a product as it is currently processed. At the local level, especially in busy units, DHM may be used more than it should be. Supplemental DHM reduces the risk and improves feeding tolerance, but does not prevent sepsis. With future developments in processing capability, the composition of donor milk and its corresponding uses and outcomes may improve.

Points of Discussion

<u>Improving the composition of human donor milk:</u>

The way donor human milk is processed makes the final product differ from MOM more than it needs to. The closer we can get DHM to resemble MOM, the closer the benefits of DHM come to MOM. It is not just the thermal processes (i.e. pasteurization) that have an impact on the constituents of DHM. The significance of the processes pre-pasteurization also need to be taken into account, together with mechanical processes such as container changes. For example, freezer storage (usually for 3 months) is associated with a decrease in substances found in milk, such as lactoferrin. The reduction of these substances could explain the lack of beneficial impact of DHM on sepsis compared to MOM, among other things. However, caution must be taken in evaluating DHM. Processing DHM causes lactoferrin

to aggregate with other proteins – and so when tested, appears to be lower that its actual amount. However, when post-ingestion, lactoferrin disaggregates when digested, and can then be expected to function as usual.

In some countries, using unpasteurized milk might be the solution to creating a better product. In Norway and parts of Germany, donor human milk is used without pasteurization. This requires more stringent testing before the milk is distributed to recipient infants, but allows the composition of DHM to more closely resemble MOM. In Norway, there is less late-onset sepsis and NEC among premature babies compared to other settings. If guidelines are developed as globally acceptable standards for DHM, it is important to take into consideration these different practices.

It us useful to determine use-cases of DHM 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, owing for example to maternal morbidity or mortality. The majority of babies receive DHM for a short time before receiving MOM, for example because it may take mothers a bit of time to produce sufficient milk to fully meet her infant's needs. The vast majority of infants receive donor milk for less than 5 days in total, and less than 100 ml in total, with many receiving just one feed of donor milk (for example, just 2ml). It is unclear if the composition of donor milk really needs to be optimized to resemble MOM when an infant would likely receive very small amounts of donor human milk for a very short period of time. Further, if units have a 'rapid advancement of enteral feeds' policy, babies have parenteral lines used as an adjunct until their enteral intake is at 120 ml/kg/day, and receive fortification very fast. While caution should be taken with infants fed exclusively DHM, the concept of requiring very small amounts of donor milk for a short period of time should be the norm, and appropriate support should be given to healthy mothers who are able to express milk so that infants can transition to MOM.

Screening

It would be beneficial to have a unified list of travel restrictions and drugs that would result in the deferment of DHM donations. Such lists take a lot of time and expertise to create. At the moment, HMBANA, CBS (Canadian Blood Services) and the European countries have different travel restrictions. In Canada, the CBS guidelines on travel restrictions are followed. Linking infectious marker screening to blood screening is very pragmatic cost-wise, since blood donation services routinely test large numbers of donors. However, there are important differences in blood-borne infectious diseases compared to that in breast milk. For example, Zika virus may test negative in blood, but may still be secreted into breast milk. The need for additional tests needs to be evaluated based on the presence of these pathogens in breast milk.

Evaluating Outcomes – measuring infant growth

Intra-uterine accretion rates require a daily growth rate of 15g/kg/day. To maximize neuro-development, this requirement goes up to 18g/kg/day.

Intergrowth charts originally assumed 27 weeks post-conceptual age as the lower-limit cut-off for premature babies. The growth charts did not cater for babies less than 27 weeks post-conceptual age. Fenton charts were used for research studies on premature babies who did not fall on the intergrowth charts. Intergrowth charts are now being modified to include the Fenton chart, and these modified growth charts could be used in future studies. The Cochrane review mentioned above uses g/kg/day, and so study results are growth-chart independent.

Key points from presentation: Global Overview and Status of Human Milk Banking

It is difficult to fully convey the precise global milk banking situation. Collecting any data pertaining to milk banking is a challenge in the absence of any coordinating global body. It is difficult to ascertain where milk banks are situated around the world, and how to access them. PATH has created a map indicating milk banking locations using their own data and field work, and estimates that there are more than 600 milk banks in 60 countries. Most of these are located in North America, Europe and Brazil, with over 250 milk banks in Brazil alone. Milk banks are scarce in the African, South Asian and South East Asian regions.

A Technical Advisory Group Meeting on human milk banking was held 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. While most milk banks adopt some of these principles, there are also milk banks that do not practice any of them.

Current infant indicators do not show how vulnerable infants around the world are being fed, or what kind of support is given the mothers of these infants. PATH has observed that up to 40% of babies in NICU settings are not getting MOM. This does not necessarily mean these babies should be getting DHM. Mothers, who might themselves be in critical care settings, may not be getting the additional support they require in providing their own milk to their babies. These issues are systems level issues, and may not relate to DHM.

In current practice, DHM is primarily 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 often relates to the mothers' inability to breast feed, medications preventing her from breastfeeding, and breast surgery. Infants may also be orphaned or abandoned, precluding them from MOM. The rates of orphaned and abandoned infants differ around the world. Outside the infant nutrition setting, DHM is 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.

With regard to infant nutrition, the current consensus is that DHM should function as a replacement for formula use, but not as a replacement for MOM, with DHM ideally used as a bridge while initiating and transitioning to full MOM. Ascertaining the appropriate use of donor milk, and whether use cases should be part of milk banking guidelines, remains an unanswered question.

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

1. A policy misalignment between the interests of nutrition (which promotes breastfeeding and the issues associated with DHM) and the priorities of newborn care (which prioritizes resuscitative measures).
2. A lack of data. We do not have comprehensive data on how babies are being fed in NICU settings world-wide to be able to understand how many babies would benefit from DHM. The current global indicators using 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 understand how infants are fed in the first days of life.
3. Innovation to improve both the quality of the final product, facilitate safety procedures, and reduce costs.
4. Lack of reliable information, in the absence of a global reference with regards to setting up a milk bank, especially in countries where such expertise does not exist.
5. Failure to integrate milk banks into broader maternal and newborn care, thus limiting their effectiveness.

Higher income countries have the resources to evaluate and adapt milk banking to their individual settings – revising policies based on experience, and trying new technologies to improve processes and costs. Many lower-resource settings around the world are new to milk banking, and do not have 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.

The processes involved in human milk banking generally include selective donor recruitment and screening, sanitary milk expression, temperature-controlled milk handling, pasteurization, 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 it 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 HMB's 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 between systems. For example, the term 'pooling of milk' could refer to both the pooling of donor milk 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 recognize the culture of human milk in that 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 donor milk is eventually used. In practice, the end-distribution of donor milk tends to be the domain of clinical staff. While conceptualizing guidance, it is important to consider both the collection and interaction with the donor, as well as the interaction with the recipient of the donor milk, and 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.

Milk banks have been operationalized in various ways. Many existing milk banks are run as non-profit organizations, but there is an increasing number of commercial milk banking models. Commercial HMB's pose an ethical issue with regards to human rights, vulnerability, equity and fairness, and quality assurance and safety.

In terms of structure, milk banks may be centralized – with one large, centralized milk bank then distributing milk within a region, or decentralized, with smaller milk banks distributed across the region.

The facility may be community or hospital based, and may further 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 as a whole. 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.

It would be beneficial for milk banks to reframe their performance indicators to reflect an integrated health system, moving away from the volumes of donor human milk collected to the achievement of an exclusively human milk diet for infants as an indicator of success. DHM would 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 by governments when a government aligns its policies to promote baby friendly hospital initiatives (BFHI) in hospitals and enforcing 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.

Sustainable funding is an issue with milk banks. Milk banks are 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. These milk banks tend to be independent of the health system, and may not be known to the ministry of health of 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 procedure responsive to the local setting, is more sustainable in the long-run.

Human milk itself is classified very differently around the world, which leads to differences in the legal frameworks governing human milk use and differences in operating procedures. Countries tend to advocate for the benefits of the way they have classified human milk. This complicates determining a unified regulation system for human milk. The most commonly seen 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 (previously classified as tissue): MPHO's tend to be regulated more tightly, but there tends to be more trust in the resultant product.
3. Based on use as a nutritional therapy

4. Undefined – this usually means to indicate that human milk is in a class of its own, and does not fall into previously defined categories. The regulations applied to it may then be a hybrid based of several suitable categories.

There is no global oversight of human milk banking. More established organizations, 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 regards to human milk banking, with a national network of human milk banks. Brazil also exports this model, providing outreach to other Portuguese- and Spanish-speaking countries in a program managed by the Ministry of Foreign Affairs. They have since provided support to at least 25 countries.

There is a long list of knowledge gaps around policy and regulation, technology and innovation, the impact of human milk banking systems, the medical, technical and nutritional issues pertaining to human milk banking, and the financial issues related to human milk banking, where guidance may be helpful. These are further elaborated in the full background document.

Points of Discussion

Managing Complexity

Understanding the practice of milk banking internationally is a complex endeavor. One way of simplifying the process of understanding the safety issues related to HMB is by developing a clear hazard profile of DHM. Every country that banks DHM would have needed to recognize the clinical hazards of donor human milk, and would have applied a set of processes to that hazard such that the resultant risk to their intended recipient is deemed acceptable. Countries may have entirely different processes to manage the same universal hazards based on what is acceptable to their population. It would be powerful to have guidelines that embraces differences in practices while referencing commonalities, and outlining the minimum and maximum quality standards that need to be met. A danger of the 'pick & choose' approach – indiscriminately putting together parts of HMB different processes to then create a 'new' one – is the disconnect between the practice, the process, and the hazard that is being managed.

It is important to look at the optimal use cases of donor human milk, 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 donor human milk might be used inappropriately. Gathering both information about the use and mis-use of donor human milk as well as determining minimum standards is difficult in light of knowledge gaps perpetuated by the lack of funding to do research in

this area. Investing in both empirical research and in the development of donor human milk related technologies may be the key to providing solutions for what is presently deemed a challenge. For example, the current pasteurization system has been developed for bovine milk – but investment in a pasteurization system developed specifically for human milk may result in a higher quality product post- pasteurization. Keeping this in mind, while establishing minimum standards may be critical, it is also important that any guidance provided is not too specific so as to not impede embracing new technologies and information to improve processes in the long run

While acknowledging the complexities of implementing an integrated milk bank, the operational aspects of HMB at the level of the hospital need to be simplified to be feasible in a wide-variety of settings, including low-resource settings. In rural hospitals in Africa, milk banks have been set up safely using low-cost pasteurizers 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 – allows 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 without 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.

Terminology and Definitions

Not only are MOM and DHM very different in their composition, but there is also a large variation between DHM products. It is also important to be precise when referring to raw, pasteurized or retorted DHM. 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 parental feeds would be different from a low-birth weight infant without any other complications.

Human milk is unique in that we are still discovering what human milk of the 'highest' quality should constitute. In the past, it was assumed that no bacterial growth meant DHM was of high quality, but the current discourse challenges that, questioning instead if destroying the microbial content of milk actually makes it less safe. 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 selling human milk, and whether this should be permissible.

Regulation of DHM

Given the complex profile of DHM, existing regulatory frameworks are imperfect proxies for the regulation of DHM, with DHM overlapping into various categories within the legal framework. It may be useful to consider classifying DHM into the category in which it is most appropriately regulated, 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.

Integration of Human Milk Banks into Health Systems and Lactation Support Frameworks

In South Africa, being a mother and baby friendly hospital is a pre-requisite to opening a milk bank. This is a good way of ensuring milk banks are set up in places where mothers would be supported, and that DHM is not used out of convenience when actually inappropriate.

Donor human milk often becomes a substitute for MOM, the supply of which is constrained by inhibitions on parental visitation in many developing countries. A common infection control measure involves prohibiting parents from entering NICU's, 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. 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, it is too late for lactation and past the point that skin-to-skin would help infants against sepsis. Since the hospitals use human milk instead of formula, they justify that the use of DHM is consistent with WHO guidelines.

In India, a site recognized as a leading model in family participatory care in the NICU involved parents extensively in the care of their high-risk infants. This was facilitated by housing mothers close to the NICU, and enabling fathers to transport MOM to the NICU. This addresses one of the barriers of transporting MOM to NICU's. NICU's then 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.

Guidance looking at the processes required to acquire MOM, embedding milk banks within a lactation support program, as well as the logistics for handling milk thereafter would be helpful to facilitating these processes.

Reconceptualizing pasteurized vs. raw milk systems

The use of pasteurized and unpasteurized within a single healthcare system does not need to be mutually exclusive. Germany runs a dual system using both pasteurized and raw milks. Raw milk is reserved for the smallest and sickest infants, and pasteurized milk for babies who are less ill. Although this may seem counter-intuitive initially, the hazards are managed so that raw milk is as safe as pasteurized milk by requiring additional assessments before being declared safe to use. Milk that does not meet the criteria allowing it to be safely used as raw milk is then pasteurized, and provided to other infants.

Mother-infant relationships

A unique aspect of DHM in contrast to other MPHO's is that DHM does not just disrupt processes related to infant nutrition, but also disrupts the mother-infant dyad – both on the part of the recipients of DHM, as well as the donors. Understanding how DHM could affect the relationship between mother and infant, although complex and incompletely understood, is crucial and should be reflected in guidance related to HMB. For example, is DHM only appropriate when mothers can simultaneously be present and also 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 natural breastfeeding possibilities.

Key points from presentation: Overview of Operating National Tissue Banking Programs

For a long time, DHM was classified as a food, since babies are in essence fed with it. However, the more we know about human milk, the more we realize it also has characteristics of a nutritional therapy and an MPHO. Appropriately classifying human milk remains a challenge. The significance of considering DHM an MPHO lies in the medical aspects of DHM use. DHM is used as a product to improve healthcare, and there is a consensus in practice about the common ethical values between DHM and other MPHO's. Common ethical issues affecting both DHM and other MPHO's involve the lack of equity, socioeconomic inequalities, and the increasing trend of commodification.

Donation is, overall, an altruistic act, with accepted reimbursement made of 'reasonably-incurred' expenses. The 'no trade' concept is often embedded in national legislation, but in reality, this practice is questionable. Plasma donors are paid by the volume of plasma donated, semen donors are also

reimbursed, and gamete donors are often sourced for 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 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 of 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 commercialization of human milk and the ability to make a profit is an emerging issue, and an increasingly widespread one. It is important to consider the circumstances, if any, when for trade profit 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.

With regards to policies and legislation, what is common among all MPHO programs these days are concerns about risk, and a risk-based approach. This is reflected in the agreed importance of quality and safety, and has stimulated work in developing standards for MPHO's. While very sophisticated standards can be developed, what is really of importance to regulatory bodies is the minimum required standards. Standards essentially involve good manufacturing or laboratory practice. Adherence to standards can be different when they are created by the relevant associations, adopted voluntarily and self-regulated, or when they are created by the regulatory bodies and imposed as a requirement. This is an importance nuance, as problems often arise when institutions choose not to comply. While regulations are not necessarily willingly accepted by everyone, they are welcomed because they ensure that the system is transparent and that products delivered are of a certain quality. There can be issues with regulation when the expectations are too high and an institution is already struggling to exist. Finding the exact level where these regulations need to be placed so that they are beneficial without being unreasonable is key.

Access will also remain inequitable unless there are policies and appropriate governance in place that understands the demand, ensures a sufficiency of supply, and provides sufficient funding 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 are likely to suffer financially in the absence of further government support unless their subsequent operational model is cost-recovering.

Commercial practices also have an impact on equitable access. Inducements to donors and aggressive marketing tactics jeopardize the altruistic ethos of any banking program, and ultimately impact equitable access when recipients are unable to afford higher product prices.

As it is unclear how DHM should be classified, it is also then unclear how DHM should be regulated. Classifying DHM previously as a food also precluded it from important discussions on the ethical issues raised above. In India, breast milk is classified in a class of its own, with a separate set of legislation around it. Voluntary standards do exist for HMB, but there is a lack of transparency around whether this is adhered to in practice. It is likely that HMB's are non-compliant with professional standards, let alone ethical standards.

In creating policies and legislations, it is important to keep in mind harmonizing standards while not stifling practice through increased costs.

There is a large fear, often out of proportion, when it comes to risks involved in donor selection. It is accepted that the risk of MPHO use is never zero, but it is still hard to resist instituting potential safety measures when possible. This may result in unnecessary 'safety' measures added to donor selection guidelines. MPHO donation programs screen donors extensively against medical issues, issues affecting the quality and safety of the donated organs, tissues or cells, and issues impacting donor welfare. This is done in a transparent process that is well-documented. The donor selection procedure is organized such that selection is consistent. This process includes a number of elements that reduce risk, and involves taking informed consent, a medico-social interview and physical examination, blood screening, repeat serology (in living donors), and relevant ancillary investigations. While the details may differ slightly based on the requirements of different tissues and cells, all donor selection programs would include these elements. There may also be additional considerations that are environment-specific (for example screening for Zika virus in Brazil) and tissue cell-specific (such as serum motility or quantity per sample), that are used as a donor screening requirement. When these criteria are not met, the donor is excluded or the sample discarded. The selection criteria must be clear, based on the over-arching requirements of the MPHO program. An additional challenge for milk banks compared to other tissues is the impact of donation on the donor's own milk production – the recruitment and selection of donors may impact feeding choices for the donor's own babies. The ideal donor recruitment procedure for HMB specifically has yet to be established.

Registries have been extremely useful in certain MPHO programs, and have contributed to the success of bone marrow donation programs. Collating data allows us to understand donation trends, supply and demand, and medical capacities which ultimately contribute to improvements in technical and medical practices. However, maintaining a registry is a resource-intensive process both in terms of manpower and finances. It is important to understand the exact purpose of the records being kept, and how this data is being used. It is also important that the registry is kept updated, with relevant and coherent data being supplied, so that it does not become obsolete. There are many registries with high rates of non-conversion, where people intend to donate but fail to update the registry of changes in details and are then uncontactable when called upon. For this reason, the registry itself also requires appropriate governance. It is difficult to motivate people to contribute to a registry in the absence of any direct benefit to themselves. The Australian cornea registry is an excellent example of a well-functioning registry, and is maintained by working in collaboration with clinicians who provide regular feedback.

There are no known registries of potential donors to milk banks. The processes in milk banks are rarely digitalized, hampering the collection and organization of data and limiting data-sharing between institutions and countries. It is not known if any data is being collected by milk banks. If data is indeed being collected, it is not known if the definitions of parameters being measured are shared across milk banks. For example, to one milk bank, a 'discard rate' could refer to milk discarded because it did not pass microbiological scrutiny. To another milk bank, the 'discard rate' could refer to all milk discarded for any reason, including milk that has gone out of 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 about donations vary significantly between MPHO's. Organ donation is best known among the public, followed by bone marrow, cornea and gamete donations. There is poor public awareness on tissue donation, of which milk banking is a subset. The reasons for varying levels of awareness range from funding to lobbying. There is no standard formula when it comes to raising public awareness. Communication strategies differ based on the MPHO in question, financial resources available and competing interests, but experience has shown that it is best if messages could be simple and clear, and promote some form of action. On the other hand, misconstrued messages could lead to the commodification of the MPHO, which is not appropriate.

In the UK, milk banks have been unfortunately described as the nation's 'best kept secret'. Most people believe that milk banks have been closed. The low level 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 savvy around social media. While there

can be difficulties stimulating interest around non-mothers, amongst families, milk banking is immediately relevant to their needs.

Quality assurance and safety is imbued in all MPHO programs, and is a means of risk management. If the necessary 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 program should be in operation at all. Quality management systems should be in place based on relevant policies and work standards. They outline, direct and record each significant step in the MPHO program, from sourcing to the release of the MPHO for utilization. MPHO's need to be handled in Grade A environments. This involves understanding environmental contaminants that may impact the quality of the final product. Although human milk may have been collected outside the milk banks control, it is the duty of milk banks not to contaminate it any further. The current reality of milk banking is that DHM may have travelled a long distance before reaching the milk bank. For quality assurance purposes, it is important that record-keeping spans from the donor to the end-user even after DHM has left the milk banking facility. On top of a quality management system, there must also be a quality assurance program – validating and verifying that the entire operation is in conformity to the decreed standards and that expected outcomes are being met. This would involve engaging both internal and external auditors.

There is no universal operational model that reflects the realities of all milk banks. The best operational model is one that allows that donation, banking and utilization will occur according to ethical values and the best possible safety and quality standards, delivering targeted results according to socio-economic and funding realities. Milk banks should plan such that these essential elements are eventually part of their basic operational models. The entire cycle of donation, transplantation, governance, regulatory oversight, infrastructure and the like requires an appropriate funding model. Funding models may vary from large investments by health departments to careful cost recovery models. HMBs are also likely to engage a range of public, private not-for-profit, and for-profit players in their daily operations (for example, by engaging a courier service to deliver the donor milk), so there must be a clear understanding of the role of each entity involved and policies surrounding their engagement. The required budget for running a milk bank is difficult to discern 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, but it is important that milk banks are run efficiently, and, even if not-for-profit, have sound business plans in place.

The infrastructure and human resources available to milk banks can similarly vary from a sparse room at the back of a hospital to large, well-equipped and well-staffed facilities. What is important is that the facilities should reflect and fulfil their purpose. If a milk bank starts small, it is important to be aware of and plan for future growth. Operational models should 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 work flows where possible. There is not a lot of guidance about the layout of milk banks, and designing a milk bank can initially be very challenging.

Staff must be available in adequate numbers, be adequately trained and competent at their required duties. There are a number of milk banks that are currently relying on a single person or very few people to run, which poses a challenge to the maintaining the operations of the milk bank. Although the provision of certain services required of the HMB may be contracted to 3rd parties, the HMB still takes final responsibility for the quality of DHM.

Most frameworks and standards for MPHO include procedures for biovigilance and the evaluation of outcomes. This involves understanding where products are distributed to, and how they are then used. The interaction with the end-user is intrinsic to determining what the best possible quality of the MPHO needs to be, and whether changes in processes are necessary. To enable biovigilance, MPHO's need to be traceable by having unique identifications so that the MPHO can be traced from each donor to each recipient. The traceability of milk has been improved by including DHM into international coding, and it is now included in the ISBT 128 system. Pooling practices in milk bank pose a challenge for traceability as milk from a number of women is pooled and then distributed to a number of infants. This makes recalling a product when there is a failure in processes a difficult task, and is a risk that milk banks need to carefully consider. It is worth looking at whether global outcome registries need to be created, and considering how and to whom adverse events should be shared. The reporting process in the event of an adverse event needs to exist before any such issue occurs. These events should be reported to professional associations as well as the regulatory authorities, which have the role of following up and putting suitable measures in place. The outcomes of DHM use are often only measured in the clinical situation, which might be far from the milk bank. For other MPHO's, maintaining outcome registries have been crucial in documenting outcomes. For example, a failure in the way a tendon was being processed in the UK was only identified when a group of patients with failed tendon grafts were reported 5 years later to an outcome registry.

Points of Discussion

<u>Issues with procurement and procurement procedures</u>

There is a small number of manufacturers of equipment for milk banks. Equipment may also vary considerably enough as to not be easily comparable. There is a virtual monopoly on some equipment, notably pasteurizers. This poses a challenge for ensuring fair procurement 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 pressure cookers to generate steam). If alternative solutions are being utilized, it is important to validate that using these methods delivers the required quality standards. For as long as the required quality standard of DHM remains undetermined, questions around the required processes will complicate choosing or designing appropriate equipment that meets those needs.

Commercial pasteurizer companies are currently also not obligated to validate their equipment, and are not held to any particular standard. In terms of guidance, it would be useful to have a validation protocol, so that the institution in charge of procurement can hold suppliers accountable. The equipment needs to further be verified to function as part of the in-house processes, and so should further be validated to function appropriately in the local environment.

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 must always be enough staff to keep the program 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 programs 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.

Physical layout of human milk bank

It is important to identify the purpose of the human milk banking space, its location, and its surrounding environment. Identifying the purpose 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 shower change area, and a milk expression and collection area. 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 gynaecological 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 banks design.

Registries

If a web-based registry is being developed, it could also consider integrating other related health management systems. 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 data captured is crucial to ensuring meaningful outcomes.

Exploitation and ethical issues:

Milk banks have a role in preventing exploitation and mitigating the ethical issues related to DHM. Little is known about the motivation, experience, and characteristics of women donors. It is important to consider whether the donor milk 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. It would be worth contemplating the alternatives for them, and not to deprive women and babies of milk that would be useful to themselves. However, this also presents a conflict of interest. It is important for larger agencies (such as government health departments or food departments) to also reflect issues related to and preventing the exploitation of women in their national policies, 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 for exploitation can be operationalized.

Quality and Safety

There is a tendency for a 'safety creep' in MPHO processes, where it is difficult to resist adding an additional action on the basis of 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 must be a balance between safety and reasonable actions to achieve a safe product and outcome. With MPHO's, there is an acknowledgement that no matter how much we do, there is always a remnant risk. A completely safe DHM product would be impossible to issue. How then do we determine how safe is safe enough, and what safeguards are sufficient?

Doing as much as possible with regards to safety allows a milk bank to more accurately determine the cause of an adverse event when it occurs, and 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.

From a microbiological safety point of view, breast milk is unique amongst MPHO's in that there is usually a critical control point of heat treatment with pasteurization. At the same time, the effects of remnant toxins, spore-forming bacteria, lipid-oxidation and other processes may remain even post-pasteurization. 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 donor milk 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 DHM is as safe as possible, but not prohibitively so.

Identifying knowledge gaps and challenges in human milk banking based on background presentations

In defining the need for international guidelines, it is 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 process of developing a product varies depending on the type of product. Developing technical guidelines is a time and resource-intensive process, requiring a thorough review of the current research, further research to fill knowledge gaps, and possibly pilot studies. Other products could be just as beneficial, and quicker to develop – for example, creating a policy brief. To develop a meaningful and timely product, we must first ask what the most pressing issues in HMB that require a response are.

Although some countries consider breast milk to be a food product, DHM is donated as an MPHO. There has been a member state request for the MPHO framework, of which DHM can be seen to be a part of. The further development of DHM would be part of the implementation of specific products within the MPHO framework. However, member states tend to focus on more conventional MPHO products such as blood, plasma and organs.

There may be a strategic advantage for DHM adopting the MPHO label. Health programs tend to receive more support than food programs, including in considerations in policies and with regards to ethical approaches. On the other hand, classifying DHM as a tissue may impose challenges based on current policies surrounding MPHO's. 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 more closely comparable to other forms of enteral feeding (as opposed to parental nutrition, which is more processed and more overtly medicalized). 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 utilized 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.

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 to any classification system. Although coming up with a unique framework for DHM may solve these issues, navigating multiple legal systems would be a huge and complicated endeavor.

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 or not to follow this based on their particular context. It is of greater importance globally that agreed 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 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 chose to classify donor human milk in a certain way, whether as a food, an MPHO or an unclassified product.

Further to issues on quality and safety, there is recognition that the majority of milk banks are currently being established in an unregulated manner. There is growing public recognition on the importance of human milk. The absence of regulations in milk bank does not then discourage 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 donor human milk use.

There is a consensus on the need for overarching governmental regulation. A suggested guidance could involve the WHO clarifying the differences within human milk bank 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 for countries looking to start their first milk banks.

Developing guidance at the moment is limited by the lack of data around HMB. At present, evidence only supports the use of DHM for NEC and infants with very low birth weight. To further complicate the lack of data, human milk is often used as an undifferentiated term in studies, referring to both mother's own milk and donor human milk, 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, a collaboration with the Spanish government, that may be useful to replicate 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 states clearly the definitions of everything being asked for, so that definitions are harmonized and data is made comparable. This transfers the responsibility of data collection to member states, and usually gets a response rate of 80%. Milk banks could similarly be registered in a registry under the oversight of the WHO using a standardized data collection form. An overarching global body or global alliance has been in 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 would be just one component. Limitations in the capacity to manage data-collection by countries may also affect the quality of 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 that would also serve HMB. An example would be capturing neonatal mortality in neonatal ICU's, since neonatal mortality is a statistic routinely captured by health departments as one of the sustainable development goals, and a reduced mortality rate is also a desired outcome of human milk banks. Another alternative is working with 3rd party sources such as NGO's to collect the required data. There is a lot of potentially relevant data already being captured, for example global infant feeding indicators, that has not been purposefully designed to capture the target population of HMB. It may be wise to develop a working group focused on defining the data required, and determining how indicators from data already being collected can be improved to meet the data needs of HMB. 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 is 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 a second round of data collection. Collecting data on this smaller scale allows meaningful representation of regional perspectives.

DHM is unique as a product in that the donors and recipients are both mother-infant dyads. This must be kept in mind when considering quality, safety and ethical aspects, such that the impact on both members of each dyad have been carefully thought about. We would then go beyond the interest of the recipient infant to, for example, stay safe from transmissible diseases, but also 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. Inadequacies in breastfeeding and lactation support need to be addressed together with the need to supply DHM, with the priority in human milk feeding being on MOM. Milk banking should be situated in the context of improving access to MOM, such that it supports breastfeeding and lactation outcomes rather than supersedes it.

Access to DHM when mothers are unable to produce enough of their own milk is a real problem. In an optimal feeding systems framework, donor human milk would only be used when needed. However,

even in resource-rich countries such as the US, there are significant disparities in the use of both MOM and pasteurized DHM. In hospitals serving lower income families, rates of human milk feeding are low primarily because mothers are not informed about the benefits of MOM. At the same time, infants do 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 NICU's in the US currently have access to DHM. In lower income and lower resource countries, feeding infants an exclusive diet of DHM in the absence of MOM presents an additional moral and ethical issue when DHM is administered unfortified.

Guidance would ideally address human milk banks 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 must be the priority.

A systematic approach to human milk banking, where milk banks are integrated into larger health systems are more sustainable and beneficial, but not common. One barrier to this is that it is hard to make a clear economic case for the return on investment on human milk banks to funders at the national level. This may change if the economic benefit was more apparent.

An RCT in Paediatrics [5] on the cost effectiveness of supplemental donor milk versus formula for very low birth weight infants (a complete cost analysis of 400 babies randomized to DHM or preterm formula, with healthcare costs followed up and tallied for 18 months on) showed that although donor milk was not cost-saving, it also did not cost more than formula. The reason for that 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. 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 have shown that although 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 and bronchopulmonary dysplasia, so there is more robust economic data on the advantages of MOM that has not be shown with DHM.

To defend the investment case, attempts have been made at modeling the long-term impact of DHM when used optimally as a bridge. This has so far proven a challenge to model, because of the complexity of other confounding interventions.

Although DHM should ideally be used as bridge to MOM, this is difficult in practice. 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. As a consequence, overall lactation rates initially improve on the unit. However, once the use of DHM becomes more established, there tends to be less of an emphasis on MOM, with correspondingly less support and volume.

It is important to be clear on the need for DHM, and the direction of any standards on HMB. There is acknowledgement of the need to exercise caution with HMB, so that DHM does not misleadingly usurp optimal feeding with MOM. At the same time, there is a need to ensure that human milk banks that are currently running are operating safely.

Legitimizing DHM with WHO standards will encourage countries to focus on this product, and may distract resources. 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.

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 discussion.
ii. Milk banks should be situated as part of the framework of optimal newborn nutrition, with DHM used as a bridge until the use of MOM could be facilitated.
iii. It would be beneficial to strategically place milk banks under the MPHO framework.
iv. There needs to be further consideration of how DHM should be best used, what constitutes appropriate use and overuse, who it should be delivered to, and at what quantities.
v. There is a huge lack of data, especially relating to issues of quality and safety.
vi. Definitions of key terms used in milk banking are not unified, including the term ‘donor human milk’ itself.
vii. It is important that process management and policies are instituted at the national levels, with safety aspects built in longitudinally into the process.

Working groups were thus formed to explore the following:

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

Each group was tasked to discuss the issues, challenges, research gaps, potential minimum standards, and potential global guidance or tools needed as pertains 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 a human milk bank should tie into efforts to increase human milk and breastfeeding rates, rather than be a standalone goal. A global issue at the moment is ensuring governments have the ability to support sustainable, integrated milk banks, which involves financial ability as well as evidence-based interventions to ensure infants can get MOM whenever possible. In addition to the health benefits to an infant, the presence of high human milk and breastfeeding rates will provide the donor human milk necessary to grow and sustain a milk bank. Governments should also be aware of the threat of commercialization of DHM.

Another challenge in integrating milk banks is the lack of health care provider knowledge on how to apply and utilize 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 on human milk banks as they seem more impressive, but tend to be less willing to support a mother's own lactation, which may actually 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 in breastfeeding or human milk started to define relevant concepts. For examples, 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.

There is no consensus as yet on what constitutes optimal nutrition. One way of conceiving optimal nutrition is as a hierarchy of options, with MOM at the top of the hierarchy, followed by DHM and then formula. Alternatively, human milk as a whole could be seen as 'optimal', and formula an alternative when human milk is not available. How these options should be rationalized remains an open question. Optimal could also be perceived in terms of context. For some infants, MOM is simply not available as an option, and so can never be 'optimal'. The nutritional needs of sick, vulnerable and well babies may also differ, and need to be catered to. It is aspirational for health systems to aim for MOM as optimal feeding, but it may not be practicable for this to be exclusive.

The situation in which MOM is not available is not a fixed a category that can be clearly defined, but is instead a malleable category that requires an investment of resources to optimize. There must be recognition that it is not possible to completely alleviate situations where MOM is absent. Although challenging, this is also a concept that must be described in any document or guidance on human milk banking.

At the moment, pasteurization is generally assumed to be part of the standard processing of DHM. This assumption needs to be challenged. There is growing evidence of the harms of pasteurization in terms of the quality of the resultant human milk. A balance needs to be made between 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 low- and middle-income countries (LMIC), where the nutritional and bioactive profile of retorted milk may be less than optimal. It would be ideal to look for solutions that would allow the achievement of high levels of safety without DHM going through pasteurization. Screened unpasteurized DHM is one way of maintaining an optimal nutritional profile while also maintaining safety. If pasteurized DHM is used, the concept of 'pasteurization' needs to be clearly defined. Variance in the process of pasteurization affects the quality of DHM. This may be impacted by advances or access to technologies. This also affects the interpretation of studies relating to pasteurized donor human milk (PDHM). The process of pasteurization cannot be assumed to be equivalent, both between studies and in comparison to technology as used today.

The term vulnerable is another term that requires clarification. 'Vulnerable' should be broadly interpreted. Although the evidence for PDHM is for LBW babies with NEC, there are other vulnerable infant populations separated from their mothers. These infants are not preterm, and who are not getting good evidence-based breast-feeding support and care. This includes infants undergoing surgery, infants with cardiac defects, infants with HIV positive mothers, and infants who are orphaned. Keeping the mother-infant dyad in mind, vulnerable mothers also have risks to lactation that other mothers are not going to have, and special attention should also be paid to their care to ensure adequate milk volumes.

Very low birth weight infants are separated from other vulnerable infants in that there is evidence supporting the use of PDHM in them, whereas there are research gaps in the use of PDHM in other vulnerable infants. VLBW infants are also more likely to be in an NICU, and more likely to be separated from their mothers. Both infants and their mothers tend to be vulnerable in this population.

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

Minimum Standards

i. The focus of human milk banks needs to be on the different needs of all vulnerable and sick infants, not just pre-term infants.
ii. Human milk banks should preferentially be situated 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)
iv. There must be context-dependent considerations of the ethical issues relating to different standards of care.
v. As a pre-requisite to initiating a milk bank, high quality, evidence-based lactation care should be in place. Suggested human milk metrics to gauge this includes the following:
    a. More than 75% of mothers of both term and vulnerable infants should achieve early breastfeeding or milk expression.
    b. More than 75% of 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 health care 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 no evidence to support this practice at present. RCT's in developed countries have not shown a significant effect in sepsis reduction with PDHM, likely because they have low baseline sepsis rates. It is possible that PDHM may be shown to decrease sepsis rates in areas where the incidence of sepsis among neonates is higher, as it is in low- and middle-income countries. However, there is as yet no research to support PDHM use to prevent 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.

The role of DHM in evidence-based optimal nutritional care is currently lacking among vulnerable infants who are not pre-term or of low birth-weight. 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 that have self-reported that term babies and otherwise well babies who are not volume restricted thrive on pasteurized donor milk, 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.

Implementational research on effectively setting up milk banks and outcomes that are meaningful to measure is currently unavailable. In terms of infant parameters as an outcome, care must be taken to measure more than conventional growth standards – an infant may have a micronutrient deficiency, but still appear to grow well, although it may suffer on other measures, such as 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. There is evidence that introducing PDHM increases breast-feeding rates and human milk feeding in the short term. However, there are suspicions of a 'PDHM-creep', where PDHM eventually supersedes MOM as it is easier and more convenient for institutions to access and use PDHM than it is to support MOM.

Cases and appropriate uses:

Given the current evidence, it is clear that PDHM should be used in the absence of MOM for VLBW infants to decrease the incidence of NEC. There is potential for the use of PDHM in other vulnerable infants, even as we acknowledge the absence of current research supporting this. 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 systematized research evaluating its effects in all infant groups of specified weights, ages and medical conditions. It would be prudent to ask ourselves how far we need to prove this. DHM should be classed as an alternative to MOM, and would be most fairly compared to other such alternatives. At the present moment, the alternative is formula milk. DHM, especially when pasteurized, raises some open questions and remains different from breastfeeding and MOM, but its use may still be appropriate even if it has not been clearly proven yet.

Additional Suggestions to Global Guidance

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

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

For mothers and infants at risk, the following is suggested:

1. Pump early (within one hour), 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 breast-feed in the longer term)
4. Ensure sick and vulnerable infants are exposed to mom's own milk during 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, 6 months post-hospitalization.

The following SWAT analysis may be useful to governments and departments of health in their evaluation of donor human milk:

Strengths	• Next best thing after MOM • 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 SDG1, SDG 2, SDG 3, SDG 5,SDG 10
Weaknesses	• Depends on milk bank infrastructure/readiness • Lack of lactation specialists • Lack of data on DHM compared to MOM • Lack of understanding of the place of DHM in optimal infant nutrition • Indications unclear • Requirement for fortification if longer term • May have cultural and religious barriers
Opportunities	• Improve human milk feeding overall, with an aim to increase breastfeeding rate to a specified percentage • Strengthen breast feeding 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 health care workers and physicians • Sustainability of milk banks

	• Cost • Donor recruitment • Donor exploitation • Lack of support to mothers • Lobbying from formula companies / Conflicts with commercial interests • Overuse of donor milk • Equipoise contested in order to answer research gaps • Profit • Unintended harms e.g. DHM becomes the easier default • 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 commercialization.

Regulation

Regulatory issues pose a huge challenge to countries. These challenges include the appropriate classification of human milk, the complexities of regulating informal milk sharing, and policies that protect the import and export of human milk.

As a minimum standard, regulatory bodies should be responsible for ensuring the quality of donor human milk 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 donor human milk. 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, regulatory bodies could require all human milk banks 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 human milk banks, specifying 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 rules of financial engagement (for example, stating whether for-profit or formula companies are allowed to contribute to the financial operations of human milk banks), and creating auditing 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 breast milk and its components for other purposes and its corresponding ethical issues. One such use is the biobanking of breast milk for its stem cells, which a donating mother may request a human milk bank 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 to develop their own context-dependent regulatory systems.

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 regards 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 human milk banks are meant to serve. This would include neonatal feeding and lactation support indicators, to give an accurate picture of whether babies require donor human milk or whether systems supporting MOM need to be strengthened.

Doing a randomized 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 in human milk banking. 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, which spent 6 months collecting data prior to initiating its milk bank, with post-implementation data collected 6 months from 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 how milk 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, including the standardization of data collection for feeding pre-term and sick infants.

Global guidance could call for the identification of 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 indicators used to track feeding and lactation support for vulnerable infants.

Advocacy

In practice, established health professionals, including those specialized 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 the misuse of DHM, with infants who need DHM not receiving appropriate care. Guidance that situates issues of access to DHM within the framework of human rights may improve advocacy for human milk banks. To ensure the political commitment of governmental organizations, guidance could suggest that member states have a defined policy and strategy on improving neonatal health by contributing to optimal nutrition, specifying that this includes the use of donated human milk.

Appropriateness and demand

The inappropriate use of DHM and the inappropriate establishment of human milk banks may result in the unnecessary diversion of resources into a milk bank 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 including supportive breastfeeding policies, safety and quality regulations, and an awareness of the need

for human milk banks. Inappropriate use of DHM also increases the potential for exploitation, and undermines breastfeeding and the provision of MOM.

Countries should have clear policies on the appropriate use of DHM, and state prerequisites for the establishment of a human milk bank. 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 with each other. It can be challenging to coordinate these milk banks, and their competing interests and competition for regional access may be inappropriate and inefficient. Countries may optimize efficiency by integrating milk banks into the larger healthcare system, and linking them to breast-feeding 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 estimated volumes of DHM required determined, 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.

Commercialization

Commercialization is a major issue. On the one hand, commercialization has benefited milk banking by bringing in funding to drive innovation and research. On the other hand, it can be exploitative and tends to be orphaned from human milk banking programs and larger health systems. Commercial milk banks tend to promote their product as a safer alternative than that from a non-profit milk bank, even though their processes are not transparent and the quality of their product is not known. This also undermines public trust and confidence in non-profit milk banking models.

A policy brief is urgently needed to outline the issues surrounding the commercialization of human milk banks, its position within the International Code of Marketing of Breastmilk Substitutes, and the protections that countries should consider.

There are specific issues in the marketing of DHM that mimic or are analogous to inappropriate marketing of breast milk substitutes. Based on experience, the Code as practiced within countries is not the international Code but a national adaptation of that code that is then adopted into law. Although DHM is not a breast milk substitute, the provisions of the Code should still apply to it. This introduces

confusion at the layer of government regulators, who may not fully understand the classification of this product. From a legal perspective, commercial human milk bank entities would 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 of regulated in some manner.

Governance

There is no consensus on what actions leadership in HMB should provide. The range of responsibilities potentially includes advocacy work, engaging in policy development and implementation, monitoring of human milk banks 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. At present, the directorate of milk banking institutions tend to have a background in nutrition. A collaborative effort involving experts in child and newborn health as well as experts in biosafety would be appropriate.

There are many commonalities between milk banking guidelines, although there are some differences which need to be resolved. The European Milk Banking Association has created regional guidance by reviewing 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 to fall 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 can then be reviewed by an international working group, which can later reconvene to review and harmonize practices.

The milk banking community has identified the need for a global alliance of milk banks, bringing across different sectors of healthcare on both the national and international level, 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 may need to 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. At the present moment, there is a lack of data supporting the necessity of DHM. Government authorities also need proof of the use of DHM – this would likely 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 nested 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 donor human milk. In India, citizens identified to be living below the poverty line are identified and allowed to access DHM without any out-of-pocket cost, 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 could be part of the guidance for countries trying to establish a milk bank.

Although milk banks can be quite costly to run, DHM is replacing another costly product – formula milk. If the operations of human milk banks are publicly supported, its 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 human milk banks in a country should be a foundational activity prior to initiation. Documentation of such a need would both 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.

Working Group 3: Quality and Safety

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

Practices between milk banks vary considerably. 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 deprioritized, and issues relating to HMB often do not fit into available funding strategies.

The intent of these processes is to optimize the final product. We do not yet have a clear idea of what optimal means for donor human milk, and have not yet been able to clearly characterize it as a product to be able to define this. In an ideal situation, the composition of raw human milk and the optimized product from a human milk bank should be identical. Practically, this product may not be possible, and DHM is then always 'suboptimal'.

One limiting step in optimizing DHM is the inability to reliably analyse donor human milk, and hence accurately characterize it. It is uncertain if current measurements of components of DHM are accurate or meaningful. There are few specialized laboratories that are capable of measuring the macronutrient profile of DHM accurately. Most milk banks employ commercially available technical equipment meant for use in the dairy industry. For example, the MIRA milk analyser, that uses infra-red technology to analyse dairy milk, is used at present by some milk banks to analyse human milk. These milk analysers have not been validated for use in human milk. This is also an ethical concern in that resource-poor countries are investing in machinery to analyse human milk that may have no positive bearing on the process.

Some milk banks are expected to provide information on protein and caloric content by the dieticians and neonatologists who order DHM. This practice is a legacy of formula milk, in which nutrient values can be clearly calculated and milk volumes ordered accordingly. This is an expectation of the current health system, even though we are unsure of the clinical significance of these numbers. Whether or not this practice should have a place in HMB needs to be evaluated. For many parts of the world, DHM is used as a therapeutic intervention to save lives, and the differences in caloric values are less relevant than the benefits an intervention with DHM may provide.

Even if human milk could be accurately analysed, optimizing it would be 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 necessarily reflect what the infant is able to absorb. Understanding which components of the milk should be measured and interpreting it is also complex – for example, DHM may have normal measurable fat content, but this may be affected by the reduction of lipase in the same sample. Fortifying milk in terms of calories and proteins may be ignoring the most important parts of DHM, which are its bioactive components. In some scenarios, milk is being rejected as a result of not meeting certain caloric

or protein content requirements. This milk may be perfectly adequate for another population of infants, or for infants who only require short-term supplementation with DHM, for whom nutrition is not the primary benefit of this supplementation.

Although we are unable to define optimal, it is the responsibility of the 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 the nutrient profile of a nutrient when compared to 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 the first factor affecting milk quality. The constituents of human milk may also vary on a day to day basis. Milk will not be uniform in spite of similar practices among milk bank. Understanding present practices would be a starting point in setting the initial standards from which milk practices may later improve upon. Understanding and improving recruitment processes should also be part of this process.

Since we are unable to define or achieve optimal DHM, it could for now be defined as DHM with the highest retention of as many beneficial properties, and the with the lowest pathogenic activity. DHM might need to be reconceptualized from being a singular product to being a range of human milk products sourced and processed in different ways to meet the needs of defined end-users. Optimizing the product would then be about making it effective for that purpose, not making it perfect.

Much of the research on human milk tends not to take into consideration the larger health system. There must be an emphasis on situating human milk and human milk banks within the health care system, and for HMB to include high-quality lactation support and care. In assisting mothers, some of the quality issues around DHM will be addressed. For the majority of babies, DHM is meant to be used as a bridge until babies are able to 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. This would enable the recruiting and matching of donor mothers to recipient infants, to provide donor milk that would be most similar to the mother's milk we are trying to mimic, and most beneficial to the recipient infant's needs. At the same time, while trying to optimize DHM, there needs to be awareness of children receiving suboptimal MOM, for example when their mothers are malnourished, and also providing them the 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.

While DHM poses a potential safety threat depending on its quality, screening and processing procedures, DHM can also be considered a contributor of safety to neonatal care. DHM contributes a beneficial natural microbiome to the infant, and allows the avoidance of formula use and its

consequences. This should be taken into account when weighing safety and quality issues. In the absence of clear targets, the safety and quality of DHM rests on ensuring the proper processes are in place, and are duly followed. For example, in preventing the transmission of pathogens, milk banks should consider how to screen donors and/or milk samples, how internal processes are set up to prevent microbial contamination during handling, and whether pasteurization is necessary given its negative effect on the beneficial natural microbiome of human milk. Aspects of safety and quality protection also come from ensuring the milk bank is adequately staffed, and that staff are trained and competent in the duties required of them.

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 can also be marked as points of quality control. The output of this process would be a form of guidance in itself. 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 testing 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 to do with safety, there is a vast variation in practice, with different methods and samples used to different results. An analysis and validation of current practice would be useful, with guidance on the safe range of practice. Global guidance should consider a call for alternative means of processing breast 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 HACCP process is included by India in their milk banking guidelines. 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, but the most appropriate product for a particular infant at the right time and conditions, and under 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 that all infants should have access to optimal nutrition, and that MOM as an optimal nutrition source should be supported as much as possible, wherever possible. Beyond MOM, it is difficult to define definitively which nutritional products should be prioritized, given that there is no standardization when it comes to processing donor human milk. This results in processed donor human milks having vastly different compositions and nutritional properties, sometimes to the detriment of the recipient child.

At the same time, an array of knowledge gaps impeding the formulation of best practices with regards to donor human milk banking were identified. These include the lack of evidence regarding optimal processes such as pasteurization and fortification, the lack of medical evidence for when the use of donor human milk is superior to formula milk (apart from neonates at risk of necrotizing enterocolitis or feeding intolerance), and difficulties in measuring outcomes. Various practical challenges with the establishment of donor human milk banks were also identified. These included the use of donor human milk as a convenience product instead of MOM, and the exploitation of human milk donors in profit-driven human milk banks.

Given the expansion of human milk banking particularly in LMIC's, evidence-based guidance is urgently needed. Closing the research gaps will be an important next step driving the process of developing recommendations, minimum standards and guidance tools for the donation, use, storage and distribution of human milk.

References:

** These references were specifically raised in the presentations/discussions. A footnote referencing the background papers individually for more comprehensive references will be added once it is clear how to reference/publish them.

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