SUPPLEMENT ARTICLE

Infant Feeding Practices, Dietary Adequacy, and Micronutrient Status Measures in the MAL-ED Study

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The overall goal of The Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) cohort study is to evaluate the roles of repeated enteric infection and poor dietary intakes on the development of malnutrition, poor cognitive development, and diminished immune response. The use of 8 distinct sites for data collection from Latin America, sub-Saharan Africa, and South Asia allow for an examination of these relationships across different environmental contexts. Key to testing study hypotheses is the collection of appropriate data to characterize the dietary intakes and nutritional status of study children from birth through 24 months of age. The focus of the current article is on the collection of data to describe the nature and adequacy of infant feeding, energy and nutrient intakes, and the chosen indicators to capture micronutrient status in children over time.

Keywords. dietary intake; infant feeding; MAL-ED; micronutrients.

Malnutrition and micronutrient deficiencies during childhood persist as public health problems in low- and middle-income countries, and the burden of death and disability attributed to these factors remains high [1]. It has long been understood that child malnutrition results from the complex interplay of multiple factors at the national, community, and family levels [2]. However, for the individual child, it is the interplay of 2 immediate factors—the adequacy of their dietary intake and the frequency and severity of illnesses, particularly diarrhea—that influences growth and the risk of malnutrition [3, 4]. More recently, attention has been drawn to the central role that gut integrity may play in child health; importantly, it has been suggested that chronic intestinal inflammation and mucosal damage moderate the effects of illness and poor diet to affect risk of malnutrition and survival [5, 6].

The goal of The Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) cohort study is to evaluate the interrelationship between repeated enteric infections and dietary intake as they influence the likelihood of malnutrition, poor vaccine efficacy, and poor cognitive, social, and behavioral development [7]. The crux of the hypothesis being tested is that the driver in this interrelationship is the nature and timing of the enteric infections that negatively impact gut function. For this hypothesis to be tested, it is crucial to obtain high-quality measures of the nature and timing of infections as well as the

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nature, quality, and sufficiency of dietary intake. In this article, we describe the various methods chosen for the MAL-ED study to capture the dietary intakes of children across the 8 sites (in Bangladesh, Brazil, India, Nepal, Pakistan, Peru, Tanzania, and South Africa). Micronutrient status may mediate the outcomes of growth and development, and thus, the indicators chosen for their assessment in the study are described as well. As part of the broader MAL-ED Network [7], a Nutrition Technical Subcommittee was formed with members from each site. The subcommittee developed the protocol, data collection instruments, and training materials, and oversaw the implementation of this component of the protocol.

CONCEPTUAL FRAMEWORK FOR ASSESSING DIETARY INTAKES

The first 2 years of life involve profound changes in diet for the young child. At birth, the newborn needs to elicit its own nourishment and does so in episodic fashion. Only during this initial postnatal period does one food, breast milk, provide complete nutrition. It is recommended that an infant be exclusively breastfed for the first 6 months of life, and to then be gradually introduced to nutritious and safely prepared complementary foods that meet the gap in nutrient requirements left by breast milk at around that age [8, 9]. Research has documented in various settings the likely nutrient requirements that need to be met from non–breast milk foods during this time period [10, 11]. Over time, as infants further develop gross and fine motor skills, they move away from specially prepared mashed or softened foods and consume only the family diet, and at some point in time, they no longer receive breast milk.

Thus, the challenge for the MAL-ED cohort study was to identify the optimal methods for characterizing the adequacy of dietary intakes in children over this important transition in each of the 8 study sites. Based on our knowledge of the feeding transition and on factors that affect dietary intakes, we identified the following key dietary exposures (Table 1) to assess (1) breastfeeding (from initiation to complete weaning); (2) prelacteal feeding and early interruptions in feeding (0–1 month); (3) weaning pattern (usually thought of 0–6 months and the transition away from exclusive breastfeeding); (4) diet quality, in terms of the frequency of feeding and the quality and diversity of complementary foods (introduction of complementary foods through 24 months and beyond [complete weaning]); and (5) adequacy of energy and nutrient intakes. We also considered that specific food components of the diet could influence local gut function apart from their role in providing nutrients to be absorbed and utilized by the body, and that it would be important to be able to characterize food intakes in addition to energy and nutrient intakes.

Table 1. Key MAL-ED Dietary Exposures

Dietary Exposure	Source of Data
Breastfeeding	
Prelacteal feeding	Enrollment interview
Timing of initiation	Enrollment interview
Exclusivity (exclusive, partial)	Biweekly and monthly interviews
Age at complete weaning	Biweekly and monthly interviews
Infant feeding practices	
Age at introduction of non–breast milk liquids, semisolids, and solids	Biweekly and monthly interviews
Age at regular consumption of semisolids and solids	Biweekly and monthly interviews
Dietary intake	
Energy, macronutrient, and micronutrients	Monthly 24-h recalls
Nutrient adequacy ratios	Monthly 24-h recalls
Probability of intake inadequacy	Monthly 24-h recalls
Overall dietary quality	
WHO indicators (frequency, diversity, minimal acceptable diet, intake of iron-rich foods, intake of vitamin A–containing foods) (6–24 mo)	Biweekly and monthly interviews Monthly 24-h recalls
Mean adequacy ratios	Monthly 24-h recalls
Biomarkers of dietary intake	
Plasma retinol	7, 15, and 24 mo
Plasma zinc	7, 15, and 24 mo
Plasma ferritin	7, 15, and 24 mo

Abbreviation: WHO, World Health Organization.

METHODS FOR DIETARY EXPOSURES

We utilized multiple instruments to characterize the dietary exposures of the children in the MAL-ED cohort. First, at the time of enrollment (at birth or before the infant was 17 days old), questions were asked of the mother regarding breastfeeding initiation and the provision of prelacteal feedings. Second, when field-workers visited the families twice per week to detect and characterize enteric infections, they asked questions to characterize breastfeeding practices and the consumption of non–breast milk foods. Although the questions regarding illness covered the entire period since the last visit, the feeding questions focused on the prior day, and followed the pattern of questioning often used by the Demographic and Health Survey (DHS) [12]. This allowed us to frequently assess the exclusivity [13] and intensity (number of feedings during the day and at night) of breastfeeding on a regular basis, and in the case of the nonbreastfed or mixed-fed infant the adequacy of milk feedings. We also queried about the feeding of common weaning foods and liquids across the sites: water, tea, coffee, fruit juice, semisolids or solids (eg, grain-based porridge, rice, root-based

preparations, banana), and fermented drinks or foods, as well as the provisioning of peanuts, peanut spreads, and onions, garlic, or shallots. In addition to allowing us to describe early infant feeding practices, the collected information can also be linked temporally with data on stooling patterns, as well as gut function tests such as the lactulose-mannitol test (see Kosek et al [14] in this supplement).

Third, we conducted a more extensive interview each month with the mother or caregiver. The nature of the interviews shifted over time. For infants 1–8 months, we utilized a qualitative 24-hour recall or food frequency approach modeled on a DHS questionnaire. For infants aged 9–24 months, we switched to a quantitative 24-hour recall approach so that we could derive estimates of energy and nutrient intake from non–breast milk foods as the child transitions toward complete weaning. The qualitative 24-hour recall data were complementary to the data obtained from the twice-weekly reports (described above), but queried over a wider range of foods, including types of fruits and vegetables, grains, roots, and specific animal source foods. As before, we queried the mother or caregiver regarding the diet of the child on the day prior to the interview. This type of data has proved informative for examining breastfeeding practices, the emerging adequacy and diversity of the child's diet, and growth in young children in developing countries such as reported in Arimond and Ruel [15]. It also provides the requisite information for quantifying the new World Health Organization indicators for assessing the quality of infant and young child feeding: (1) timely introduction of complementary foods; (2) frequency of feeding; (3) diversity; (4) both frequency and diversity (minimal acceptable diet indicator); (5) intake of vitamin A–rich foods; and (6) intake of iron-rich foods [16].

From age 9 months onward, our primary interest is in quantifying the usual intake of energy and nutrients from complementary foods, as well as characterizing specific eating practices such as the provision of energy-dense complementary foods (eg, pap, gruel, or the inclusion of foods from animal sources). The decision to begin to quantify consumption of non–breast milk foods at 9 months was based on 3 considerations. First, although we expect infants to receive non–breast milk foods prior to and around 6 months, the amount of non–breast milk foods consumed is small and would not justify the use of the 24-hour recall. Second, by 9 months of age, we expect infants on average to be receiving approximately 300 kcal per day from non–breast milk foods [11], and thus variation across children in energy and nutrient intakes of non–breast milk food becomes a key dietary exposure of interest. Third, other aspects of the MAL-ED protocol (Lactulose-Mannitol testing, child developmental assessments) created an additional time commitment for the families when their infants were 6–8 months of age; thus, beginning this new, more involved collection of dietary data at 9 months also had practical advantages.

Dietary intake information collected via repeated 24-hour recalls represents a preferred collection technique to quantify energy and nutrient intakes of young children over time [17]. Strengths of this technique include the following: (1) It is an open-ended technique adaptable across study sites; (2) individuals trained in the technique exist worldwide; (3) it is applicable to any age group and can be adapted as children age; (4) it allows for recipe collection and additional information about the feeding context (eg, meal structure, dietary patterns); and (5) it permits the incorporation of new information for new analyses as science evolves. Although the use of direct weighing techniques is arguably ideal to overcome errors in subject recall and portion estimation, the cost and intrusiveness of having data collectors in the household each month for 12-hour periods, given the scale of the project, would be unacceptable. Thus, our approach was to collect a single 24-hour recall per child each month. Because of within-subject (ie, day-to-day) variation, it is well known that 1 recall does not provide a highly precise estimate of usual nutrient intake at any given time point [18, 19]. The precision of an estimate of nutrient intake is inversely related to the amount of within-subject variation (often expressed as $s^2_{within}/s^2_{between}$) of nutrient intake, which is a function of food availability, dietary sources for that nutrient, and other factors in a specific population [18, 19]. Essentially, the greater the variability, the greater the need for replicates to achieve a given level of precision [18, 19]. Because the MAL-ED study is longitudinal, there are 16 measures available for each child from 9 to 24 months, which can be combined to capture more precise intake information overall or over specified time points (eg, 9–12, 13–18, or 19–24 months). The precision of an individual's energy intake averaged from 4 dietary recalls is quite high, and although the precision of each nutrient intake estimate based on 4 recalls is likely lower (because of greater $s^2_{within}/s^2_{between}$), we will have information on its precision for each child.

To enhance the data collected, we also created a system of secondary recalls, to be collected 2–7 days following the monthly recall. This was done through a randomization procedure in which each child was randomly allocated to have a secondary recall done following 1 study visit between 9 and 24 months of age. Thus, at each age (ie, month), a sample of 10–20 secondary recalls provides estimates of $s^2_{within}/s^2_{between}$ variation in energy and nutrient intake per study site. This information can be used to refine both group and individual estimates of energy and nutrient intakes beyond the precision afforded by the monthly energy and nutrient intake estimates.

THE MAL-ED 24-HOUR RECALL SYSTEM

For the 24-hour recall collection, we created a common form for use across the 8 study sites. We adapted forms used previously

by researchers at the Instituto de Investigación Nutricional (IIN) in Lima, Peru; at International Centre for Diarrheal Disease Research, Bangladesh (icddr,b) in Dhaka, Bangladesh; and at the University of Bergen (Norway) working in Bhaktapur, Nepal. The form was structured and prompted the interviewer to write down all food and drink offered to the child, the time and the place of consumption, whether it was raw or cooked, the amount served, and the amount left over. A separate collection form was constructed to obtain details on the recipes for preparations served to the child.

Training plans for using the 24-hour recall technique were developed by the Nutrition Technical Subcommittee for each study site following general principles [20] and key technical resources, as well as the specific level of training and expertise at the site. Local or regional experts in the recall technique were identified to help select materials, obtain information regarding infant feeding practices, and to help with the training for study site staff. There was an initial 3-day training with follow-up exercises, and further reinforcement through periodic 1-day refresher training sessions. At the study sites, most of the recall data were collected by nonnutritionists who were supervised by a nutritionist or researcher with experience in the collection of dietary data. During the data collection phase, the regular conference calls of the Nutrition Technical Subcommittee provided a forum for discussing issues, and site-specific conference calls to focus on specific issues allowed this dietary and nutrition data collection system to operate efficiently and smoothly.

Prior information regarding infant feeding at each study site dictated that data collection techniques be tailored to each study site. A prime example is the techniques used to quantify dietary amounts. At the MAL-ED sites in Pakistan and Bangladesh, weighing exercises were conducted to develop standard weights of common foods, as well as the weights associated with measuring devices and serving utensils and bowls. For the Nepal site, infants are most commonly fed small bites of rice dipped in a sauce by hand; therefore, field-workers utilized balls of dough to gauge amounts and to engage mothers in a discussion on how they feed their infants. Study sites also worked to create a profile of local utensils and implements for measuring, cooking, and serving; samples were available during interviews with the mother or caregiver to facilitate the recording of amounts fed or used in food preparation. Food models had been developed by researchers at IIN for a prior study in Peru [21], and these were replicated for use at the Peru site.

The question of the appropriate food composition database for multisite studies is complex, particularly given the uneven quality of such databases across different countries worldwide. There are multicountry studies in which dietary intake information was unified to match a single food composition database such as the US Department of Agriculture (USDA) food composition tables (eg, Merchant and Deghan [22]). Although it added complexity, early in protocol development it was decided that each MAL-ED site would utilize unique food and recipe codes and food composition tables. We decided that unique codes were necessary for a number of reasons. First, there is no universal food composition table that can be used for this study. We believed there would be an important loss of detail and information by trying to choose appropriate food codes from the USDA tables for local foods fed to young infants in the 8 MAL-ED study site countries. Second, most sites had experience using at least 1 specific food composition database and accompanying food codes and we wanted to build on local and national expertise. Third, we wanted to be able to add nutrient content information for local foods and calculate the nutrient content of preparations fed to study infants. Therefore, we embarked on a very open-ended process to characterize local foods and preparations that could be utilized in future dietary studies of young children at each site. Although some sites have strong national or regional food composition databases (eg, South Africa Food Data System developed by the Medical Research Council, or the food composition tables developed by IIN for Peru or by the Harvard School of Public Health for Tanzania), and other compiled international databases such as the World-Food Dietary Assessment System or International Minilist are available (www.fao.org/infoods), there still remains a need to utilize multiple food composition databases to impute values for missing ingredients, foods, and preparations. Therefore, for each site, we identified a primary food composition table and then secondary and tertiary sources to be utilized as needed to obtain the requisite food composition information.

One of the biggest operational differences across the MAL-ED study sites is in the collection of recipes. The need for recipe collection depends on the completeness of the food composition database (particularly for local foods), a recheck on the appropriateness of a national database for the local area, and features of infant feeding in the study population. In the South Africa and Tanzania sites, for example, relatively simple preparations (involving 2–3 ingredients) are made, and these can be captured easily on either the food recall or recipe forms. Also, there is limited variation in the local method of preparation. In other settings, such as in South Asia, rice with sauces are prepared and served daily for the family. The sauces made will vary depending on ingredient availability and other factors. Because these sauces are likely important nutrient sources, it is important to characterize them each time they are prepared, which necessitates the collection of detailed recipes of preparations at each visit. Ultimately, this level of detail will provide important information about the nature of infant feeding, dietary sources, and patterns, and should lead to improved estimates of energy and nutrient intakes.

As described elsewhere in this supplement [7], all nutritional data collected from all 8 sites are entered using a uniform data

entry system, with built-in quality control checks. The challenge of utilizing the 24-hour recall approach is the significant amount of work done postcollection to transform the collected information into a format for streamlined data entry and manipulation to produce dietary intake estimates. This work goes beyond simple checks, and requires technical expertise in the compilation of dietary data, recipe calculations, data management, and analysis, which is limited at most of the study sites. Thus, a centralized data system was developed to evaluate the collected data for complex errors, develop composite recipes and common variants, impute nutrient values, and maintain a system of documentation to create a unique infrastructure for linking the dietary data with databases used for estimating energy and nutrient intakes as well as other key dietary exposures of interest. The ultimate goal is to transfer this capability to the collaborating sites for analyses and future studies.

KEY DIETARY EXPOSURES FOR ANALYSES

An element of the central MAL-ED hypothesis focuses on the nutrient adequacy of the diet consumed by children in each site. This, together with the children's illness history, forms the key determinants of growth and its faltering. Therefore, we intend to utilize the probability approach originally developed by the USDA [23–25]. In this approach, we estimate within each site and at each age the usual intake distribution of each nutrient (adjusting the variance using the estimates s^2_{within}/$s^2_{between}$ generated from the secondary recall data), and relate this intake distribution to the corresponding nutrient requirement distribution. By doing so, we calculate the prevalence of inadequate nutrient intakes, and how it changes as children age from 9 to 24 months of age. Statistical analyses of such data to examine additional factors (eg, seasonality and socioeconomic status) will also be conducted for the MAL-ED study.

The probability approach is generally applied to groups as opposed to individuals because in such situations, replicate data within individuals are often not available [26]. However, we will have multiple measures from a child (quarterly or other relevant time period collection) enabling us to utilize these multiple measures to assign a probability of adequacy to each individual child at multiple time points for use during individual-level analyses and hypothesis testing. We can utilize the raw nutrient intake data (eg, intake on day *X* of 40 mg vitamin C), but the probability approach provides the added value of linking the raw intake data with standardized requirement distributions (eg, Recommended Daily Allowance or Dietary Reference Intake), and for inferences to be drawn regarding drivers of programs and policies to monitor and improve dietary intake throughout the world. From these analyses, we can characterize the adequacy of carbohydrates, protein, fat, zinc, iron, and vitamin A intakes (and others) as individual dietary components that may influence the MAL-ED study outcomes of interest (ie, growth, cognition, gut function, and immune response), along with information on the adequacy of energy intake.

There is also interest by the MAL-ED staff in evaluating the dietary patterns of these enrolled children as they evolve over time, in terms of diversity and quality. Composite measures will also be calculated. Importantly, we can calculate the mean adequacy ratio, which is a composite or comprehensive measure of dietary adequacy combining information on the adequacy of intake of multiple nutrients [27]. Another example is the dietary diversity scores developed by Arimond and Ruel [15]. Unique to this study is the focus on gut integrity and the microbiome; therefore, it is of interest to quantify the prebiotic or probiotic potential of the diet, as well as to consider the consumption of foods containing fructo-oligosaccharides. Characterizing these aspects of the foods consumed would involve appropriate coding and algorithm development to capture the information collected from within the 24-hour recall and other infant feeding data. The choice of the 24-hour recall method provides the study with a flexible platform to quantify energy and nutrient intakes of children over time, and the ability to conduct additional analyses and explore new hypotheses in the future.

BIOCHEMICAL INDICATORS OF MICRONUTRIENT STATUS

Micronutrient status is determined by dietary intake and by factors that affect absorption, utilization, and excretion (metabolism), as well as illness and growth. Thus, while nutrients enter the body through food (or supplements), a child's micronutrient status reflects the body's ability to respond to needs that are dependent on that nutrient. As part of the MAL-ED study, we are collecting blood and urine samples at 3 points in time (7, 15, and 24 months) to assess the micronutrient status of enrolled children at each site, and to relate these status measures to outcomes during analyses. At each time point, we are assessing iron, zinc, vitamin A, and iodine status.

For iron status, there is a well-developed literature on the need to assess multiple indicators [28, 29], and we have identified 3 key indicators for the MAL-ED study. Hemoglobin concentration (measured at the time of blood collection by the HemoCue method) is used to measure anemia, and plasma ferritin and plasma transferrin receptor are both measures of iron status [28]. By assessing ferritin and transferrin receptor, we will also be able to estimate total body iron stores [30] and we will be able to identify anemia and/or iron deficiency and characterize the body iron stores of the enrolled children at each time point. This is important as alterations in cognitive, social, and behavioral development have been associated with both anemia and iron deficiency [31]. To gauge the interpretation of these indicators in the presence of inflammation, we have also assessed

α-1-acid glycoprotein (AGP) [32]. Based on several meta-analyses, we do not expect iron deficiency or anemia to affect the growth patterns of the enrolled children [33, 34].

There is a strong body of evidence that zinc deficiency is a cause of growth faltering and malnutrition, and that zinc is a key micronutrient supporting the immune system [35, 36]. In addition, there is a growing yet incomplete literature on the association of zinc deficiency with poor cognitive, social, behavioral, and sensorimotor development [37]. Therefore, the assessment of zinc status is essential for the testing of our core MAL-ED hypotheses [7]. The assessment of AGP is also needed to interpret and adjust values in those children with inflammation per accepted guidelines [38].

Iodine deficiency is known to be a leading cause of preventable mental retardation. Although public health efforts have virtually eliminated moderate to severe iodine deficiency globally, children may still suffer from low intakes, which may negatively influence their cognitive development. In the MAL-ED study, iodine status is assessed by urinary iodine concentration using the urine samples [39] that are collected for the lactulose-mannitol test. As part of the monthly assessment, we also query the mother or caregiver regarding the use of iodized salt for cooking and consumption, which is available in each of the 8 sites.

Finally, vitamin A is a key nutrient for the immune system, and its deficiency is related to an increased risk of morbidity but not of poor growth [34]. In the MAL-ED study, we assess plasma retinol concentration, the standard indicator used in studies and surveys for vitamin A status [40]. As with iron and zinc, we will study the role of inflammation [41].

Through these 4 micronutrient assessments, we will be able to conduct site-specific analyses on the micronutrient status of enrolled children as an indicator of the nutrient adequacy of their diet, and to consider how dietary intake is related to micronutrient status. None of these indicators are biomarkers of dietary intake (for a traditional validation of our 24-hour recall data, see, eg, Bingham et al [42]), but rather concentration markers of status that may mediate the outcomes of growth and development. However, because we expect to find the diets of these children to be limited in some nutrients, we do expect to identify associations between usual nutrient intake and concentrations of ferritin, retinol, and zinc that will support the validity of our dietary intake measures.

CONCLUSIONS

A major objective of the investigations of the MAL-ED cohort study is to evaluate the roles of repeated enteric infection and poor dietary intakes on the development of malnutrition and poor cognitive development of children. The use of 8 distinct study sites for data collection from Latin America, sub-Saharan Africa, and South Asia allow for an examination of these potential associations and relationships across different environmental contexts. Key to testing study hypotheses is the collection of appropriate data to characterize the dietary intakes and nutritional status of enrolled children from birth through 24 months of age. The development of a comprehensive and rigorous data collection platform that would provide high-quality information, yet be flexible to allow implementation in all sites and shift as the dietary intakes of children changed from birth to 24 months of age, was required. The information shared here and in the supplement will be of interest to the public health nutrition community as well as to program planners and policy makers who seek to understand the nature and adequacy of dietary intakes on the growth of young children in their country or region.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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