SUPPLEMENT ARTICLE

Disease Surveillance Methods Used in the 8-Site MAL-ED Cohort Study

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Describing the early life associations between infectious disease episodes and growth, cognitive development, and vaccine response in the first 2 years of life is one of the primary goals of the Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) cohort study. To collect high-resolution data during a critical early period of development, field staff visit each study participant at their house twice weekly from birth to 2 years of age to collect daily reported illness and treatment data from caregivers. Detailed infectious disease histories will not only allow us to relate the overall burden of infectious disease with the primary outcomes of the study, but will also allow us to describe the ages at which infectious diseases have the greatest effect on child health. In addition, twice-weekly visits allow for sample collection when diarrhea episodes are identified. This article describes the methods used to collect illness and treatment history data and discusses the a priori definitions of diarrhea and acute lower respiratory illness episodes.

Keywords. diarrhea; infectious disease; MAL-ED; respiratory infection; surveillance.

A myriad of factors are associated with childhood growth and development. The Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) study [1] attempts to elucidate these factors by incorporating field surveillance, laboratory, and clinical assessments from 8 diverse field sites [2–9] using a harmonized protocol. More than 200 children per site were enrolled at birth into MAL-ED and followed for 2 years, during which time data on their health, growth, and development were collected. This article describes the field surveillance methodology and discusses some of the challenges and dilemmas of the study as it is implemented in both rural and urban settings in 8 developing countries.

The MAL-ED study was originally conceived to measure the attributable effects of diarrhea on important health outcomes, such as growth and development [1]. However, given the intricacy of the relationships between putative enteric pathogens and growth, we developed a surveillance system to quantify a variety of common exposure variables that may be associated with growth and development during the first 2 years of life. Active surveillance in the study needed to accommodate 3 goals: (1) to provide a daily illness and treatment history for the child, (2) to identify episodes of diarrhea to allow for specimen collection, and (3) to measure other ancillary exposures that are related to the primary outcomes.

Diarrhea during childhood has been associated with both short-term [10–12] and long-term growth faltering [12–22], as well as decreased cognitive development [23, 24]. Respiratory infections and fever have also been shown to be negatively associated with growth [21, 22]. Yet, there is some controversy in the literature regarding the long-term effects of diarrhea and other infectious diseases on growth, as catch-up growth is possible given

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adequate illness-free time and dietary intake [25–27]. The processes underlying growth faltering and cognitive deficits are complex. Diarrhea is one potential cause of stunting, but there are a variety of other factors that may result in growth faltering, such as other infectious diseases, inadequate diet, and genetic factors [28]. Furthermore, malnutrition may lead to higher burdens of diarrhea and/or enteric infection, requiring careful longitudinal analyses to assess [13, 29]. Yet another factor in this complex relationship is that diarrhea is an imperfect indicator of enteric infections, and asymptomatic enteric infections may play a larger role in these outcomes than has been heretofore appreciated [14, 30]. Therefore, the illness and treatment data collected over the first 2 years of life in 8 countries will be used to better understand the complex processes of growth and development, and potentially identify areas where one can intervene.

DISEASE SURVEILLANCE METHODS

Daily illness and treatment surveillance data are collected twice a week in the participant's household by trained MAL-ED field staff using the Surveillance Assessment Form (Supplementary Appendix). The Surveillance Assessment Form was translated into the local language in 4 countries (Pakistan, Nepal, Peru, and Brazil) and retained the English form in the remaining countries (India, Bangladesh, South Africa, and Tanzania); in all countries, field staff members communicate verbally with the mothers or other caregivers in their local languages. Field staff members ask the mother or other caregiver whether the children experienced any of the symptoms or took any of the treatments listed in Table 1 on each day since the last study visit. Household visits are generally made every 3–4 days; however, if a child is not visited for >7 days, surveillance data are collected only for the last 7 days (not all days since last visit).

The Surveillance Technical Subcommittee created standard operating procedures, assessment forms, and checklists for the MAL-ED study to provide general guidelines and establish minimum standards for surveillance data collection quality control activities by the field site surveillance supervisor in each country. Field supervisors reviewed all case report forms prior to submission to the local data entry center, and additional quality control screening was performed by the central Data Coordinating Center. Field supervisors or well-trained field staff conducted quality control visits to 10% of the cohort households each month, during which they asked all of the surveillance questions (Appendix). The surveillance supervisor compared their responses with the field staff case report forms, and investigated discrepancies. Overall percentage of agreement for maternal or caregiver report of any illness in the first year of life ranged from 82% to 97%, with Cohen kappa (κ) [31] ranging from 0.40 to 0.81 (Table 2). Through active management of the field data collectors, field supervisors identified further training needs, errors in stool sample collection, and data inconsistencies. In each country, the MAL-ED primary investigator and field supervisor held weekly meetings with field staff to review changes or

Table 1. Illness Surveillance Data Collected in the MAL-ED Study From Birth Through 2 Years of Age

Questions	Responses
Section A. Overall health	
Was the child sick?	No; Yes
What was the child's activity level?	Normal; Sleepy; Difficult to awaken
How was the child's appetite?	Normal or more than normal; Less than normal
Did the child vomit?	No; Yes
Did the child have ear pain/ pulling?	No; Yes
Section B. Enteric infection	
Did the child have diarrhea?	No; Yes
How many loose stools did the child pass? (loose stools take the shape of their container)	0–99
Was there any blood in the child's stool?	No; Yes
Was the child dehydrated?	No Some: irritable, thirsty, delay in skin pinch, sunken eyes Severe: symptoms more severe, with lethargy, listlessness
Section C. Other illnesses	
Did the child have an illness with a cough?	No; Yes
Was the child short of breath?	No; Yes
Has the child been ill with a fever?	No; Yes
Section D. Field staff measurements	
Field staff observe the child's chest for indrawing.	No; Yes
Field staff members take the child's respiratory rate, twice.	Breaths per minute
Field staff members take the axillary temperature if fever is reported.	Degrees Celsius
Section E. Treatments	
Did the child take oral or injected antibiotics?	No; Yes
What kind of antibiotics did the child take?	Penicillin; cephalosporin; sulfonamide; macrolide; tetracycline; fluoroquinolone; metronidazole; other; or unknown
Was child given oral rehydration salts, a prepackaged oral rehydration salt solution, or a government-recommended homemade fluid?	No; Yes

Data collected in sections A, B, C, and E are based on mother or caregiver report.

Table 2. Percentage of Agreement and Cohen κ for Maternal Report of Any Illness, Diarrhea, Fever, and Antibiotic Use in the First Year of Life, Comparing Field Data Collector Surveillance Assessment Forms and Supervisor 10% Quality Control Check

	Any Illness		Diarrhea		Fever		Antibiotic Use	
Study Site	Agreement	κ	Agreement	κ	Agreement	κ	Agreement	κ
BGD	91%	0.81	99%	0.88	97%	0.80	95%	0.80
PKN	92%	0.81	98%	0.91	97%	0.88	96%	0.87
INV	82%	0.61	98%	0.70	95%	0.58	98%	0.64
NEB	88%	0.61	96%	0.60	96%	0.59	98%	0.65
BRF	97%	0.40	100%	0.91	100%	1.0	99%	0.62
PEL	90%	0.41	93%	0.52	95%	0.50	96%	0.61
SAV	88%	0.40	98%	. . .	100%	. . .	95%	0.54
TZH	94%	0.74	94%	0.57	98%	0.68	95%	0.66
Overall	89%	0.72	96%	0.70	96%	0.69	97%	0.75

Abbreviations: BGD, Dhaka, Bangladesh; BRF, Fortaleza, Brazil; INV, Vellore, India, NEB, Bhaktapur, Nepal; PEL, Loreto, Peru; PKN, Naushero Feroze, Pakistan; SAV, Venda, South Africa; TZH, Haydom, Tanzania.

updates to forms and procedures, and to provide refresher training as needed.

Table 1, section A, lists characteristics associated with general health, including the mother's or other caregiver's assessment of whether the child experienced any illness, vomiting, or ear pain or pulling, and indicated the child's activity level and appetite. The symptoms in section B were chosen based on their relevance to enteric infection and include a mother or caregiver assessment of whether the child had any diarrhea, the number of loose stools (defined as taking the shape of the container) the child had on each day, the presence of blood in the stool, and whether the child was dehydrated. The symptoms in section C were intended to assess other illness, such as respiratory infection (eg, cough, shortness of breath, fever). Section D includes variables that are assessed by field staff including observation of indrawing and measurement of respiratory rate and axillary temperature. In addition, limited data on mother or caregiver-reported treatments are collected (section E), including antibiotic use, antibiotic type, and whether the child received oral rehydration therapy. Questions were not asked about illnesses that were expected to be less common based on local knowledge of the study sites, such as tuberculosis or human immunodeficiency virus. Information on these diagnoses may be available at the sites for subanalyses, as these infections are known to affect growth and development.

For the MAL-ED study, we used relatively standard definitions described in the literature to define illnesses. The onset of a diarrheal episode is identified when the mother or caregiver reports ≥3 loose stools in a 24-hour period, or at least 1 loose stool with blood [32]. Diarrheal episodes were separated by 2 or more diarrhea-free days [33, 34]. When the mother or caregiver report cough and/or shortness of breath on the day before the visit, field staff measure respiratory rate twice and take the child's axillary temperature. Acute lower respiratory infection (ALRI) is identified based on the presence of cough and/or shortness of breath plus high respiratory rate [35]. The average of the 2 respiratory rates is used, and is considered high based on the age of the child (<2 months of age: ≥60 breaths/minute; 2 to <12 months of age: ≥50 breaths/minute; ≥12 months of age: ≥40 breaths/minute) [36]. ALRI episodes are separated by at least 15 ALRI-free days [35]. Fever is defined as an axillary temperature >37.5°C. Children are referred to medical care based on MAL-ED site-specific recommendations, which at a minimum include the following symptoms: identification of ALRI, axillary temperature >39°C, passage of ≥8 loose stools in a 24-hour period, bloody diarrhea, or severe dehydration.

METHODOLOGICAL AND DEFINITIONAL DILEMMAS

Visit Frequency

Surveillance methods to assess diarrhea illness frequencies are based on a subjective report by the mother or caregiver of diarrhea. The accuracy of this information is dependent upon a number of factors—for example, the rapport the field data collector has with the mother or caregiver and frequency of household visits. A higher visit frequency will result in improved caregiver recall [37], as well as a greater likelihood of collecting diarrheal stool samples, respiratory rates, and temperatures, all of which are collected only on the day of the visit. Increased frequency of surveillance visits from 2 to 3 times per week would increase the likelihood of diarrhea sample collection or ALRI identification. However, the cost of the stool processing would also rise, and visiting the household more frequently is a greater burden on the enrolled family. Daily illness data collection is considered ideal; however, daily visits to the household for 2

years were not considered feasible from a logistical or financial perspective. Ultimately, we chose to visit households 2 times per week as this level of surveillance produces reasonably complete and accurate illness data. Although we fail to collect some diarrheal samples and identify some ALRI episodes, we assume those that are missed are of short duration and therefore less likely to have long-term effects on health.

Diarrhea Definition for Community Surveillance

Diarrhea is a symptom of an underlying enteric dysfunction, and can be caused by a variety of pathogens, including bacteria, viruses, protozoa, and helminths. In the MAL-ED study, the identification of diarrhea should be indicative of days when stools were unusual, and act as an indicator of enteric dysfunction. The definition of diarrhea used in this study, ≥3 loose stools in a 24-hour period or at least 1 loose stool with blood present, provides a good combination of sensitivity and specificity [32]. Some researchers have suggested using 3 diarrhea-free days to separate episodes [32, 38], but several of the MAL-ED sites have high diarrhea burdens and requiring 3 diarrhea-free days may merge distinct episodes. In addition, increasing the number of diarrhea-free days required before a new episode begins would increase the frequency of prolonged (7–13 days) and persistent (≥14 days) diarrhea.

The diarrheal definitions we used are standard in the literature [32, 33, 38]; yet, we also know that infants who are primarily breastfed produce mostly liquid stools. For this reason, in the future, we may want to adjust our definition of diarrhea based on age or breastfeeding status to specifically explore loose stools as an indicator of infection in very young breastfed children. In addition to age and breastfeeding status, the MAL-ED study also collected microbiologic data for monthly and diarrheal stools that we can use to identify the surveillance definition of diarrhea with the greatest likelihood of pathogen identification. Sensitivity analysis of the definition of diarrhea in the early months of life among breastfed children, with pathogen identification as an indicator of infection, will help us determine whether our a priori diarrhea definition is sufficient for use across all ages, or if we need to alter our definition for use in the first 3–6 months of life.

ALRI Definition

Identification of ALRI (eg, pneumonia) in a field setting is challenging, and chest radiograph and blood or sputum cultures were not available in the MAL-ED study sites. We estimate that approximately 10%–20% of the children identified with ALRI in this study have clinical pneumonia. However, this ALRI definition (presence of cough and/or shortness of breath plus high respiratory rate) is commonly used to identify children in resource-poor settings who may benefit from treatment [35]. This method for field identification of ALRI may provide an overestimate of ALRI prevalence across the 8 MAL-ED study sites, but will give us an overall idea of respiratory burden.

CONCLUSIONS

Using harmonized protocols at 8 study sites, the MAL-ED cohort study is collecting detailed information about infectious disease burden and treatments in the first 2 years of life. Detailed longitudinal illness histories allow us not only to describe the overall illness burdens, but also to describe the ages at which infectious diseases have the greatest effect on long-term health. Regarding treatments, we can control for and explore the effect of caregiver-reported antibiotic treatment and oral rehydration solution on child health. Given that mothers or caregivers were advised to seek medical care when severe symptoms were identified, we might expect that these children will be healthier than unstudied children; however, even with fewer severe manifestations of illness, we expect to see relationships between infectious disease and our other outcomes of interest. Daily surveillance data will be used to explore the complex relationships between infectious diseases and all other aspects of child health included in this comprehensive study, including gut function, dietary intake, vaccination, growth, and cognitive development.

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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