

Establishment of the MAL-ED Birth Cohort Study Site in Vellore, Southern India

Sushil M. John,¹ Rahul J. Thomas,² Shiny Kaki,² Srujan L. Sharma,² Karthikeyan Ramanujam,² Mohan V. Raghava,³ Beena Koshy,⁴ Anuradha Bose,³ Anuradha Rose,³ Winsley Rose,⁵ Anup Ramachandran,² A. J. Joseph,² Sudhir Babji,² and Gagandeep Kang²

¹Low Cost Effective Care Unit, ²Department of Gastrointestinal Sciences, ³Department of Community Health, ⁴Department of Developmental Pediatrics, and ⁵Department of Child Health, Christian Medical College, Vellore, India

The Indian Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) site is in Vellore, Tamil Nadu, in south India and is coordinated by the Christian Medical College, Vellore, which has many years of experience in establishing and following cohorts. India is a diverse country, and no single area can be representative with regard to many health and socioeconomic indicators. The site in Vellore is an urban semiorganized settlement or slum. In the study site, the average family size is 5.7, adults who are gainfully employed are mostly unskilled laborers, and 51% of the population uses the field as their toilet facility. Previous studies from Vellore slums have reported stunting in well over a third of children, comparable to national estimates. The infant mortality rate is 38 per 1000 live births, with deaths due mainly to perinatal and infectious causes. Rigorous staff training, monitoring, supervision and refinement of tools have been essential to maintaining the quality of the significantly large quantity of data collected. Establishing a field clinic within the site has minimized inconvenience to participants and researchers and enabled better rapport with the community and better follow-up. These factors contribute to the wealth of information that will be generated from the MAL-ED multisite cohort, which will improve our understanding of enteric infections and its interactions with malnutrition and development of young children.

Keywords. birth cohort; India; malnutrition; MAL-ED.

The Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) Network is conducting a multicountry, longitudinal prospective cohort study on the etiology, risk factors, and interactions of enteric infections and malnutrition and the effects of these factors on child growth, cognitive development, and vaccine response. The 8 MAL-ED cohort sites are epidemiologically and geographically diverse and comprise low-income populations; they are located in Bangladesh, Brazil, India, Nepal, Pakistan, Peru, South Africa, and Tanzania.

The strengths of longitudinal studies lie in their ability to document the natural history of outcomes over time and to elucidate temporal and possibly causal relationships among variables. Although expensive, long, and difficult, cohort studies largely overcome the problems of recall and can be used to investigate multiple exposures and determinants with a low possibility of selection bias, recall bias, and confounding [1, 2].

MATERIALS AND METHODS

The 2005–2006 Indian National Family Health Survey 3 (NFHS 3), a nationally representative survey, showed that 48% of Indian children <5 years old were stunted, 43% underweight, and 20% wasted [3]. It was estimated that in India about 54% of deaths in children <5 years old were related to malnutrition, and approximately 70% of children aged 6–59 months have some level of anemia [3]. Given these alarming statistics and a large population that contributes to nearly one-fourth of all

Correspondence: Gagandeep Kang, MD, PhD, Department of Gastrointestinal Sciences, Christian Medical College, Vellore, Tamil Nadu 632004, India (gkang@cmcvellore.ac.in).

Clinical Infectious Diseases® 2014;59(S4):S295–9

© The Author 2014. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/ciu390

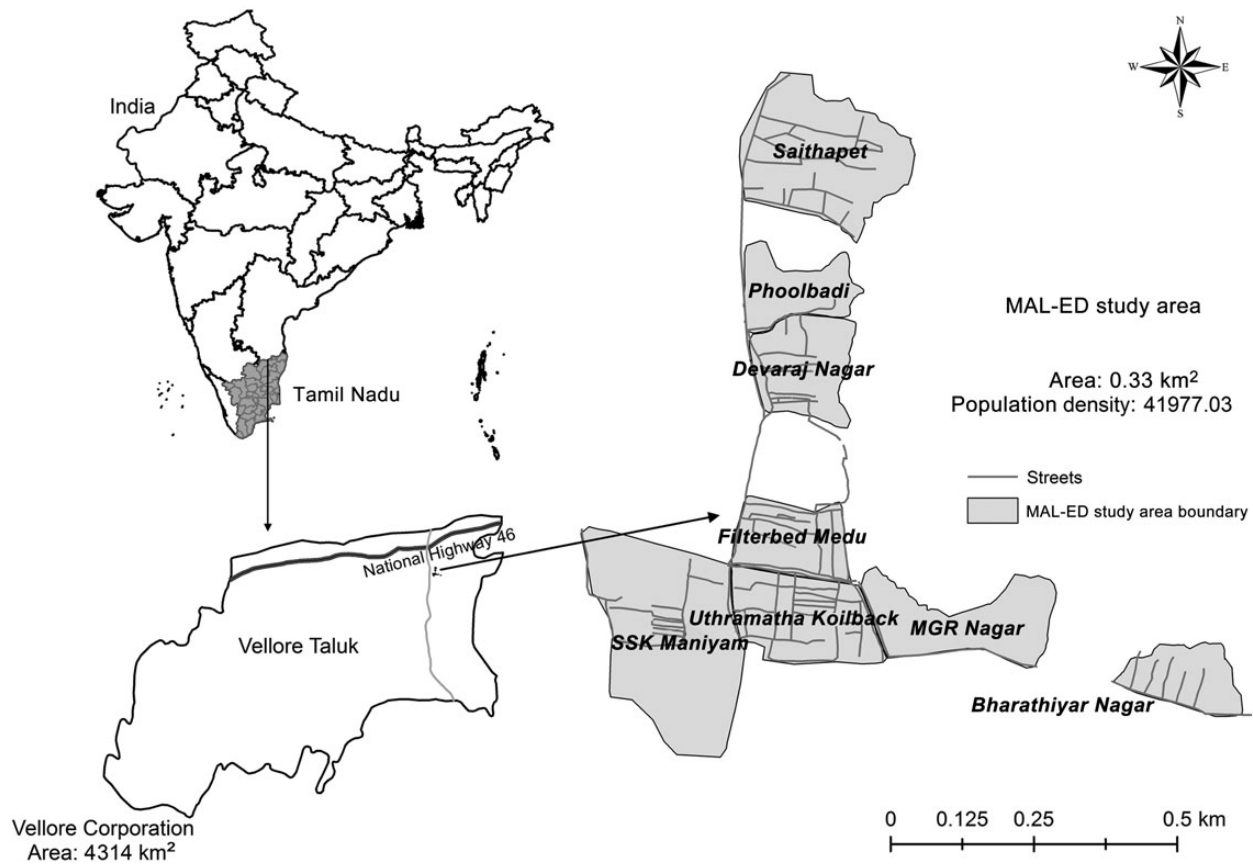


Figure 1. Location of the Vellore MAL-ED study site in the geographic context of Southern India. Shading represents the study areas, with the main streets indicated by black lines.

deaths and malnutrition in children <5 years old worldwide, the Indian cohort represents an important part of the MAL-ED study.

The Christian Medical College, Vellore (CMC), is located in the southern Indian state of Tamil Nadu and has many years of experience and expertise in setting up and following cohorts for various studies, in particular the documentation of infections and morbidity and growth [4–6]. However, CMC has not participated in a multisite cohort study with standardized methods. In this article, we describe the establishment of the MAL-ED study site and its relationship to the surrounding community and discuss the need for specific approaches.

MAL-ED India Cohort Study Site

The MAL-ED study site is located in Vellore, a city with a population of approximately 500 000 inhabitants about 130 km from Chennai, the capital of the southern state of Tamil Nadu and the nearest large city. The climate of Tamil Nadu ranges from dry subhumid to semiarid. The state has 3 distinct seasons: advancing monsoon with the southwest monsoon from

June to September; the northeast monsoon period from October to December; and the dry season from January to May. The language predominantly spoken is Tamil, and the main religion is Hinduism (89%); Muslims and Christians comprise 11% of the state's population.

The CMC is a private, not-for-profit medical school and 2600-bed referral hospital. It has 1.6 million outpatient visits and 120 000 inpatient admissions annually and also provides primary and secondary care to local residents and approximately 250 000 residents of periurban and rural service areas through a range of outreach facilities.

Old Town, Salavanpet, and neighboring areas in central Vellore have an approximate population of 13 000. The CMC Low Cost Effective Care Unit provides healthcare to the 13 000 residents of this low-income urban population through field visits, clinic, and outpatient and inpatient services at a small base hospital. Because CMC personnel were aware of the basic population demographics and anticipated an appropriate recruitment and retention rate for the MAL-ED study, Old Town, Salavanpet, and neighboring areas in central Vellore were selected as the cohort sites.

Data Sources

Several service areas of CMC in Vellore were previously mapped, and a geographic database was created. In 2007–2008, a population survey and geographic information system mapping were completed in the MAL-ED study area of Old Town, Salavanpet, and contiguous areas before the start of MAL-ED cohort recruitment. A demographic survey form was completed, and geographic coordinates of each household were obtained with a hand-held global positioning system (GPS) receiver (Garmin GPS V; Garmin International). The “way points” and “track points” provided by the GPS were downloaded using GPS Utility 4.10.4 software (GPS Utility). The points were then converted to “shape files” using ArcView GIS 9 and 10 software (Environmental Systems Research). Two data entry operators performed double data entry of the demographic data collection using Epi-Info software (version 3.5.1; Centers for Disease Control and Prevention), and the 2 data sets were compared and cross-verified with the questionnaires. All data collection and entry procedures followed MAL-ED study protocols [7].

MAL-ED India Study Recruitment

For study recruitment, a team of field workers identified pregnant women and new births in the area [8]. The size of the study catchment area was chosen based on the expected recruitment of approximately 10 children per month over a period of 2 years, such that every child born within the study area had the opportunity to participate in the study. Recruitment began in March 2010 and ended in February 2012.

Establishment of a Study Clinic

A study clinic was established in the catchment area to provide a space for the intensive examinations and procedures required for the study. The lack of privacy and small size of most study households were limiting factors in conducting examinations within the homes. The study clinic is used for anthropometry, sample collection, cognitive function testing, and first-line medical evaluation and treatment. The clinic serves as the central base for all MAL-ED study-related activities and procedures for participants and study staff; central data management is done elsewhere.

Study Staff Recruitment and Training

The complex and intensive assessments of the MAL-ED study required that the study staff be both appropriately trained and monitored during the study to ensure a high and consistent level of performance and adherence to study specific procedures. For the India Vellore study site, a faculty member or co-investigator was assigned to lead and supervise each aspect of the study: field workers and supervisors and clinic staff (S. M. J.), dietitians (A. B.), data entry operators and manager

Table 1. Health indicators for Women and Children in India and Tamil Nadu

Indicator	India	Tamil Nadu
Total fertility rate per woman	2.68	1.80
Maternal mortality rate, deaths/100 000 live births	407	134
Women receiving care, %		
Any antenatal care	77	99
All recommended antenatal care	15	34
Institutional deliveries	41	90
Postnatal examination	41	91
Crude birth rate/1000 population	23.8	16.5
Crude death rate, deaths/1000 population	7.6	7.4
Sex ratio, females/1000 males	927	942
Fully immunized children (aged 12–23 mo), %	44	81
Mortality rates		
Infants/1000 live births	50	28
Neonates/1000 live births	39	19
Children <5 y old	74	35
Birth weight reported, %	34	88
Birth weight <2.5 kg, %	22	17
Conditions in children, %		
Anemia	79	72
Stunting	38	25
Underweight	46	33
Wasting	19	8

(M. V. R. and A. Ro.), psychologists (B. K.), and microbiologists and technicians (S. B., A. J. J., and A. Ra.). Study staff was hired and trained before the start of the study, and their performance was assessed and retraining provided whenever necessary before and during the study.

Ethics Review

Before subject recruitment permission was obtained from the CMC Institutional Review Board and the Indian government's Health Ministry Screening Committee.

RESULTS

The MAL-ED study area and its relationship to Vellore are shown in Figure 1. The study area is crowded with a population density of nearly 42 000/km². The main occupation of the men is daily wage labor in the local market, with work in small shops, and a small proportion are skilled laborers. Women work at home or as daily wage laborers. In general, the state of Tamil Nadu has better health statistics than the rest of India, as shown in Table 1. The data collected from the study site before initiation of recruitment enabled comparison of the recruited children and their families with the population of the whole study area (Table 2).

Table 2. Comparison of Vellore Area and MAL-ED India Cohort Families

Comparison	Vellore Area	MAL-ED Cohort Families
Educational level for head of household, mean (range), y	4.06 (0–17)	6.81 (0–18)
Highest educational level in family, mean (range), y	8.52 (0–20)	NA
Family size, mean (range), No.	4.56 (1–19)	5.70 (3–13)
Age distribution, %		
0–19	35	NA
20–34	32	NA
≥35	33	NA
Occupation, %		
Agriculture-related occupation	0.1	NA
Skilled labor	5.9	NA
Small business owner	0.8	NA
Service-related occupation	1.4	NA
High-income group/professionals	0.2	NA
Unskilled labor	33.1	NA
Not gainfully employed (including students)	58.5	NA
Type of house, No. (%) of households	Pucca in 753 (37), mixed in 628 (31), and kutcha in 666 (32) ^a	Main floor material: earth, sand, clay, mud, or dung in 14 (6), ceramic tiles in 23 (10), and cement or concrete in 198 (84); main roof material: thatch in 45 (19), tiles in 30 (13), and other in 159 (68); main exterior wall material: mud in 36 (15), cement or concrete in 190 (81), and other in 9 (4)
Rooms in house, mean (range), No.	2 (1–6)	2 (1–6) (separate kitchen in 102 households [43%])
Main source of drinking water, No. (%) of households	Public tap in 1862 (91), public bore well (hand pump) in 42 (2), public bore well (tap) in 17 (1), tanker in 30 (2), private bore well in 15 (1), private well in 5 (<1), water cans in 17 (1), and house tap in 59 (3)	Piped into dwelling in 2 (1), piped to yard or plot in 15 (6), public tap or stand pipe in 201 (86), and tube well or bore hole in 17 (7)
Cooking mode, No. (%) of households	Firewood in 1322 (65), kerosene stove in 538 (26), gas stove in 159 (8), and >1 cooking mode in 28 (1)	Kerosene stove in 89 (38), gas stove in 61 (26), open fire in 80 (34), open fire or stove with chimney or hood in 3 (1), and electric heaters in 2 (1)
Place of cooking, No. (%) of households	Outside of house in 47 (2), inside of house in 1778 (87), and separate kitchen in 222 (11)	Outside of house in 53 (22), inside of house in 180 (77), and both in 2 (1)
Possessions, No. (%) of households		
Fan	1676 (82)	223 (95)
Tape recorder	505 (25)	NA
Transistor radio	NA	10 (4)
Television	None or government provided in 1203 (59), black and white in 220 (11), and color in 624 (30)	222 (94)
Vehicle	None in 1156 (57), nonmotorized in 532 (26), motorized in 315 (15), and both in 44 (2)	Bicycle in 96 (41)
Cupboards	Steel cupboard in 4995 (53)	Cupboards in 49 (21)
Telephone	None in 1273 (62), landline in 324 (16), cell phone in 442 (22), and both in 8 (<1)	Cell phone in 198 (84)
Electricity, No. (%) of households	NA	230 (98)
Toilet facility, No. (%) of households	NA	No facility, bush, or field in 119 (51), pit latrine in 3 (1), flush to piped sewer system in 2 (1), flush to septic tank in 21 (9), flush to somewhere else in 83 (35), and other in 7 (3)

Abbreviation: NA, not available (or data not collected).

^a Pucca means brick and cement walls with a concrete or tile roof; mixed, brick and cement walls with a roof of asbestos, thatched leaves, or tin; and kutcha, walls and roof of mud, tin, asbestos, or thatched leaves.

DISCUSSION

Longitudinal birth cohort studies provide a rich source of information about antecedents of diseases that originate in pregnancy or childhood [1]. Although Tamil Nadu is not representative of all parts of India, it is not always possible to conduct a complex study in all settings. Given that previous cohort studies in Vellore [9] have shown stunting of well over a third of children in similar slum settings, the MAL-ED Vellore study site is expected to yield valuable data on enteric infections and malnutrition.

Although most indicators from the data collected are broadly similar between the Vellore population and the study children and families, it is interesting to note that between the prerecruitment survey and the end of the 2-year recruitment period, the proportion of families with cell phones increased very rapidly; by 2012, most families had ≥ 1 cell phone.

As anticipated by the study investigators, subject recruitment and the collection of specimens in young children was a challenge owing to the cultural practice of going to the mother's natal home for delivery and the first few weeks of the newborn's life. However, overall the proportion of eligible families who refused participation in the study was $<10\%$. After recruitment, retention rates were also high, with only a few families discontinuing participation, mainly because of migration out of the study area. Recognizing that participation in a longitudinal study is demanding for families, it is best to try to minimize inconvenience to participants.

Regarding the quality control of data, the most important emphasis is on proper staff training and monitoring. It is essential to select study staff with adequate skills in communication and the ability to build rapport with the community. Pilot testing of forms and surveys and staff training were extremely important though it involved cost, effort, and time. In populations with limited education and low literacy, regular communication with study participants at all levels was important. Given the level of data collection and monitoring within the MAL-ED cohort, the supervision of study staff was essential to maintaining data quality. Having a base at the study clinic that both study families and staff could reach rapidly was important for quick responses and follow-up when necessary. A system of weekly staff meetings and monthly reviews by all study site investigators ensured that updated information was available and lags in data generation was minimized.

CONCLUSION

The MAL-ED multisite cohort study will provide critical information for understanding which geographic, social, cultural, biological, and nutritional factors play major roles in physical growth, cognitive development, and immune response. The

close integration of the study sites and central teams has been necessary to ensure high-quality data. Longitudinal studies are expensive undertakings, and to fully make use of them requires careful coordination and planning. In the MAL-ED Network, the development of harmonized protocols and tools and the refinement of their use to ensure high-quality data have been at the core of network activities.

Notes

Acknowledgments. We thank the staff and participants of the MAL-ED Network for their important contributions.

Financial support. The Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project (MAL-ED) is carried out as a collaborative project supported by the Bill & Melinda Gates Foundation, the Foundation for the National Institutes of Health, and the Fogarty International Center, National Institutes of Health.

Supplement sponsorship. This article appeared as part of the supplement "The Malnutrition and Enteric Disease Study (MAL-ED): Understanding the Consequences for Child Health and Development," which is sponsored by the National Institutes of Health and the Foundation for the National Institutes of Health.

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Eskenazi B, Gladstone EA, Berkowitz GS, et al. Methodologic and logistic issues in conducting longitudinal birth cohort studies: lessons learned from the Centers for Children's Environmental Health and Disease Prevention Research. *Environ Health Perspect* **2005**; 113:1419–29.
2. Nicholson JM, Rempel LA. Australian and New Zealand birth cohort studies: breadth, quality and contributions. *J Paediatr Child Health* **2004**; 40:87–95.
3. International Institute for Population Sciences. National Family Health Survey (NFHS-3): 2005–06. Vol 1, India. Mumbai, India: International Institute for Population Sciences, **2007**. Available at: <http://www.measuredhs.com/pubs/pdf/FRIND3/00FrontMatter00.pdf>. Accessed 29 January 2013.
4. Gladstone BP, Muliylil JP, Jaffar S, et al. Infant morbidity in an Indian slum birth cohort. *Arch Dis Child* **2008**; 93:479–84.
5. Sarkar R, Sivarathinaswamy P, Thangaraj B, et al. Burden of childhood diseases and malnutrition in a semi-urban slum in southern India. *BMC Public Health* **2013**; 13:87.
6. Gladstone BP, Das AR, Rehman AM, et al. Burden of illness in the first 3 years of life in an Indian slum. *J Trop Pediatr* **2010**; 56:221–6.
7. Richard SA, Barrett L, Guerrant RL, Checkley W, Miller M. Disease surveillance methods used in the 8 site MAL-ED cohort study. *Clin Infect Dis* **2014**; 59(suppl 4):S220–4.
8. The MAL-ED Network Investigators. The MAL-ED Project: a multinational and multidisciplinary approach to understand the relationship between enteric pathogens, malnutrition, gut physiology, growth, cognitive development and immune responses in infant children in resource poor environments. *Clin Infect Dis* **2014**; 59(suppl 4):S193–206.
9. Rehman AM, Gladstone BP, Verghese VP, Muliylil J, Jaffar S, Kang G. Chronic growth faltering amongst a birth cohort of Indian children begins prior to weaning and is highly prevalent at three years of age. *Nutr J* **2009**; 8:44.