The WHO Multicentre Growth Reference Study: Planning, study design, and methodology

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Abstract

The World Health Organization (WHO) Multicentre Growth Reference Study (MGRS) is a community-based, multicountry project to develop new growth references for infants and young children. The design combines a longitudinal study from birth to 24 months with a cross-sectional study of children aged 18 to 71 months. The pooled sample from the six participating countries (Brazil, Ghana, India, Norway, Oman, and the United States) consists of about 8,500 children. The study subpopulations had socioeconomic conditions favorable to growth, and low mobility, with at least 20% of mothers following feeding recommendations and having access to breastfeeding support. The individual inclusion criteria were absence of health or environmental constraints on growth, adherence to MGRS feeding recommendations, absence of maternal smoking, single term birth, and absence of significant morbidity. In the longitudinal study, mothers and newborns were screened and enrolled at birth and visited at home 21 times: at weeks 1, 2, 4, and 6; monthly from 2 to 12 months; and every 2 months in their second year. In addition to the data collected on anthropometry and motor development, information was gathered on socioeconomic, demographic, and environmental characteristics, perinatal factors, morbidity, and feeding practices. The prescriptive approach taken is expected to provide a single international reference that represents the best description of physiological growth for all children under five years of age and to establish the breastfed infant as the normative model for growth and development.

Key words: Anthropometry, child nutrition, childhood growth, growth curves, growth references, infant feeding practices, infant growth

Introduction

The World Health Organization (WHO), in collaboration with a number of institutions worldwide, is conducting a community-based, multicountry study to develop new growth references for infants and young children, the WHO Multicentre Growth Reference Study (MGRS). The approach taken to develop the new references is fundamentally different from that taken in the past. The new approach describes the growth of children whose care has followed recommended health practices and behaviors associated with healthy outcomes. The new curves may therefore be considered as prescriptive or normative references, as opposed to traditional descriptive references based on geographically representative samples of children, regardless of feeding or other behaviors. The MGRS is taking place in six countries representing the major world regions. This effort involves about 8,500 children and combines a longitudinal study from birth to 24 months with a cross-sectional study of children aged 18 to 71 months. This paper describes the planning, study design, methodology, study organization, and field logistics, and provides an overview of the different phases of the project from its inception in 1990 to its expected completion in 2010.

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Members of the WHO Multicentre Growth Reference Study Group and Acknowledgments are listed at the end of the first paper in this supplement (pp. S13–S14).

Brief history and planning phase of the study

The origins of the MGRS go back to 1990, when the WHO Department of Nutrition established a Working Group to assess the growth patterns of breastfed infants and the relevance of such patterns to the development of growth reference data. The Working Group on Infant Growth was motivated by multiple reports in the literature documenting significant deviations between the growth patterns of healthy breastfed infants and that depicted by the US National Center for Health Statistics (NCHS)/WHO international growth reference. The report of the Working Group was published in 1994 [1, 2]. In its analyses, the Working Group also noted a number of technical problems in the NCHS/WHO international growth reference and concluded that these problems were sufficient to result in potentially harmful decisions in the nutritional management of individual infants and inaccurate population-based assessments.

The group members recommended that a new infant growth reference be developed and that subjects recruited for this purpose should come from populations whose infant-care practices approximated current health recommendations, especially those related to feeding. They further specified that participants in the proposed effort should come from multiple countries, unlike the NCHS/WHO international reference, which is based solely on US children who as infants were predominantly formula-fed [3]. The recommendations of the Working Group were subsequently endorsed by a WHO Expert Committee in 1993 [4, 5] and the World Health Assembly (WHA) in 1994 [6]. The scope and cost of such an ambitious undertaking called for international collaboration. The normative function of WHO placed it in a unique position to provide the leadership required to carry out a project of such complexity and global visibility.

Development of the MGRS protocol

Following the WHA resolution, in 1995 a WHO Working Group on the Growth Reference Protocol was established, formed by pediatricians, nutritionists, human biologists, epidemiologists, and statisticians, to prepare a protocol for the development of a new group growth reference based on an international sample of healthy breastfed infants [7–9]. For two years, this group established the framework that resulted in a protocol outlining a fundamentally new approach, prescriptive in nature. Rather than recommending an update of “how children are growing,” the group recommended that the reference describe “how children should grow.” This approach moved past the construction of a device for classifying and analyzing data and allowing the comparison of different populations, to the development of a standard (or as close to one as possible), i.e., a device that embodies the concept of a norm or target and thus permits a value judgment. Drafts of the protocol were circulated to numerous external reviewers and presented in scientific meetings and review committees, and an initiative for raising the funds for the study was launched. Reactions from the scientific community as well as from donors were very supportive. However, the high cost of implementation of the study—about 10 million US dollars—represented for some donors too large an investment for a single project. Thus, efforts to raise the necessary funds to support the MGRS have been and continue to be an important aspect of the project’s implementation.

Selection of study sites

In 1996, when the main features of the MGRS protocol were settled, we began the process of selecting sites for the implementation of the study. The need to identify sites in each of the six major geographic regions represented a second important challenge in the implementation of the MGRS. The process of selecting the study sites lasted two years and entailed evaluation of specific eligibility criteria for study subpopulations based on the study protocol. Following a presentation of the MGRS at the World Health Assembly, a number of countries expressed an interest in participating in the study. They were requested to send in responses to the checklist of criteria (table 1) documenting the source of the epidemiological data provided.

Since valid epidemiological data were unavailable for some sites to provide information for key items on the checklist, candidate groups were requested to conduct surveys to ascertain the feasibility of carrying out the MGRS. Four surveys were conducted in Asia, one in Africa, and one in the Middle East. The main objective of these surveys was to assess the growth of children living in affluent communities and identify socioeconomic characteristics associated with unconstrained growth in these populations. Information was also gathered on infant feeding patterns, mobility of the population, and other aspects relevant to the protocol. In addition to the survey information and other documentation, candidate sites were visited by members of the Working Group. The final decision about participation was made on the basis of the results of the surveys [10–12] or available epidemiological data from other sources [13], the geographic distribution of the candidate sites, the presence of collaborative institutions able to implement the MGRS protocol, and the availability of national or international funds. The description of the study sites in the six selected countries (Brazil, Ghana, India, Norway, Oman, and the United States) is presented in separate papers in this supplement [14–19] (fig. 1).
Preparations for launching the study

During late 1996 and early 1997, the Coordinating Centre, located at the WHO Department of Nutrition in Geneva, prepared the documentation and materials of the study in English, written in great detail, to be used at the study sites for the day-to-day implementation of the study. The documentation included the Manual of Operations, Measurement and Standardization protocols, study questionnaires and interviewer guides, and Data Management protocols (available on request). A training video on anthropometric techniques was prepared for the training and standardization of field staff [20], and a data management system was developed [21]. Study instruments were pretested at the Brazilian site, which served as the pilot site. Study forms and interviewer guides were translated into Arabic, Norwegian, and Portuguese and back-translated into English to ensure that the content of the questions remained unchanged. The only documentation that was developed at a later stage, owing to a shortage of funding, was that related to the Motor Development Study [22]. The late initiation of this study made it impossible for the Brazilian site to participate in this MGRS component. The protocol for the Motor Development Study was pretested at the US site.

While site selection was ongoing, local investigators in confirmed sites proceeded with the recruitment and training of study teams. The planning phase at
EACH STUDY SITE IS DESCRIBED IN SEPARATE PAPERS IN THIS SUPPLEMENT [14–19]. INTENSIVE EXCHANGES TOOK PLACE BETWEEN THE COORDINATING CENTRE OF THE MGRS AT WHO AND THE SITES TO ADAPT THE GENERIC MANUAL OF OPERATIONS TO LOCAL CIRCUMSTANCES AND TO PREPARE LOCAL STAFF FOR THE LAUNCH OF THE STUDY. PRIOR TO THE INITIATION OF DATA COLLECTION, THE COORDINATING CENTRE TRAINED AND STANDARDIZED LOCAL TEAMS IN ANTHROPOMETRIC TECHNIQUES [20], DATA MANAGEMENT [21], AND MOTOR DEVELOPMENT ASSESSMENT [22].


FIG. 1. WHO Multicentre Growth Reference Study map

FIG. 2. Timeline of the new international growth references
Methods

Study design

The MGRS design combines a longitudinal study from birth to 24 months with a cross-sectional study of children aged 18 to 71 months. In the longitudinal study, cohorts of newborns were followed for the first two years, with frequent assessments of feeding practices and growth. A longitudinal design for the first two years was needed to provide lactation support to participating mothers, assess selection biases, and provide incremental measurements for the development of growth velocity references. Mothers and children were screened and enrolled at birth and visited at home 21 times: at weeks 1, 2, 4, and 6; monthly from 2 to 12 months; and every two months in the second year. Figure 3 presents the flow chart for the longitudinal study. Mothers enrolled at screening had a two-week period to consider and discuss their participation in the study with their families. Therefore, successful recruitment was determined at the week 2 home visit. Mothers who either refused outright, who posed important restrictions on their participation ("hidden refusals"), or who were found to be ineligible were replaced in the sample. Those who left the study after this point were considered dropouts and were not replaced.

A cross-sectional design was adopted for children aged 18 to 71 months to avoid the time and cost of conducting a longitudinal study in that age range, and also because growth in this age range is more linear than for younger children. Using 18 months as the lower age limit for the cross-sectional study allows an overlap of 6 months with the longitudinal study, which provides information on the transition from supine length to standing height and facilitates the joining of the two data sets. Although the curves will be built for children aged up to 60 months, data collection is extended to 71 months to provide reliable estimates of growth at 60 months (see below). Because of the large number of children required for the cross-sectional study, two sites with small population bases (Brazil and the United States) used a mixed-longitudinal design in which some children were measured two or three times [14, 19].

The MGRS is a population-based study with well-defined catchment areas from which mother–infant pairs are recruited: the cities of Davis, Muscat, Oslo, and Pelotas and selected affluent neighborhoods of Accra and South Delhi. In all sites, recruitment of infants for the longitudinal study took place in hospitals within 24 hours of birth. The number of participating hospitals was determined to ensure that 80% or more of the population in the designated catchment areas was screened for eligibility. For the cross-sectional study, the sampling strategy was developed according to the circumstances of each site, to provide a sample of children from the same population providing newborns for the longitudinal study [14–19].

A final important feature of the study design is that it pools samples of children who represent a diversity of ethnic backgrounds. The decision to include populations from the major world regions was supported by solid evidence showing that the growth patterns of well-nourished, healthy preschool children across the world are very similar [4, 8]. The surveys conducted as part of the selection process in the developing countries participating in the MGRS demonstrated that this was indeed the case [10–12]. The formulation of a truly international reference is likely to be more acceptable for global use than a reference developed with data obtained from a single country. This procedure averts political concerns that arise from using a single country’s child growth pattern as a worldwide standard.

Eligibility criteria for study subpopulations and individual children

The eligibility criteria for study subpopulations were used for selecting the study sites (table 1). It was not necessary for the whole population from the study area to fulfill the criteria, since this restriction would probably have precluded the participation of most sites outside developed countries. These characteristics, however, had to be present among the subpopulations from which study participants were to be drawn. The mean birthweight in the target population was not included as an eligibility criterion; however, it was taken into account when selecting sites.

The eligibility criteria applied to individual mothers and children are listed in table 2. The absence of health, environmental, or economic constraints on

FIG. 3. Flow chart of longitudinal study
Growth was applied as a criterion in the selection of newborns. An objective of the surveys conducted prior to the implementation of the MGRS was to identify socioeconomic factors associated with unconstrained growth in the study subpopulation. Local criteria for screening newborns, based on parental education and/or income levels, were developed accordingly [10–12]. The feeding recommendations with which mothers were required to comply are summarized in table 3. Low-birthweight babies born at term were not excluded, since this restriction would have artificially distorted the lower centiles of the curves in the early months. The list of diagnoses of significant morbidity was developed in consultation with local neonatologists and pediatricians at each site [14–19]. Last, because smoking can affect both lactation performance and infant growth [23–25], as well as birthweight [26], maternal smoking before or after delivery was made an exclusion criterion.

The eligibility criteria were similar for the longitudinal and cross-sectional studies, with the exception of the feeding recommendations, where a minimum duration of three months of any breastfeeding was imposed as an inclusion criterion for the cross-sectional study sample.

**Sample size**

The precision of growth chart centiles is determined by several factors, of which the most important is sample size. Other relevant factors include study design (cross-sectional versus longitudinal), the timing of measurements, and the method of curve fitting. Four criteria were used to set the sample size for the MGRS: the precision of a given centile at a particular age, the precision of the slope of the median curve over a given age range, the precision of the median curve overall and the influence of data at particular ages, and the precision of the correlation between measurements in the same subjects at different ages. The last criterion is relevant for velocity references. Sample sizes were calculated for each of these four criteria, and it was found that, for each sex, a sample size of 200 for the longitudinal study and 200 per three months for the cross-sectional study would provide adequate precision. These sample sizes were to be obtained by combining data from the six sites.

The sample size calculations yielded the finding that the first few measurements, particularly birthweight, have high variance, whereas between one and four years the variance is low. In addition, limiting the study to children under five years results in increased imprecision during the fifth year. To address the imprecision of the curves at the extremes, birthweight was oversampled and the upper age limit was raised. The sample at birth was increased fourfold, and an upper limit of 71 completed months for the cross-sectional study was implemented to improve the precision of the curves throughout the whole age range of interest.

In the longitudinal study, to obtain 400 children of both sexes, 70 compliant children per site were required to complete the two-year follow-up. The number of newborns to be recruited initially depended on the proportions expected to remain compliant (with feeding recommendations and smoking restrictions) until the age of two years. Based on calculations made from available epidemiological data, the recruitment of a target sample size of 300 newborns per site was set, the only exception being the US site, where the recruitment target was 200 newborns because the expected

<table>
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<tr>
<th>TABLE 2. Eligibility criteria for individual mothers and children</th>
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<tr>
<td>No health, environmental or economic constraints on growth</td>
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<tr>
<td>Mother willing to follow feeding recommendations</td>
</tr>
<tr>
<td>Term birth; gestational age ≥ 37 completed weeks (259 days) and &lt; 42 completed weeks (294 days)</td>
</tr>
<tr>
<td>Single birth</td>
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<tr>
<td>Absence of significant morbidity</td>
</tr>
<tr>
<td>Nonsmoking mother (before and after delivery)</td>
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<table>
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<tr>
<th>TABLE 3. Operational criteria and definitions for compliance to feeding recommendations</th>
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<tr>
<td><strong>Criteria</strong></td>
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<tr>
<td>Exclusive or predominant breastfeeding for at least 4 months (120 days)</td>
</tr>
<tr>
<td>Introduction of complementary foods by the age of 6 months (180 days)</td>
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<tr>
<td>Partial breastfeeding to be continued for at least 12 months (365 days)</td>
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<tr>
<td><strong>Definitions</strong></td>
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<tr>
<td>Exclusive breastfeeding</td>
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<tr>
<td>Predominant breastfeeding</td>
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compliance was higher. This total recruitment target fulfilled the requirement that the sample size at birth be at least four times larger than the 400 required at older ages.

To provide similar measurement densities at 18 to 71 months, the cross-sectional study was designed to include the same number of children (70 per three-month period), with each child measured once. The period from 18 to 71 months covers 18 three-month periods, so the nominal sample size required was \( 70 \times 18 = 1,260 \) children per site. Adding 11% for refusals gave a round sum of 1,400 subjects per site (78 per three-month period). This target sample size was lower for the two sites that used a mixed-longitudinal design, since some children at these sites were measured more than once. Moreover, because the MGRS protocol called for minimizing the number of children participating in both the longitudinal and the cross-sectional samples, the target age interval for the cross-sectional study at the US site was restricted to 27 to 71 months [19]. To fill the gap created by the absence of children in the age range from 24 to 26 months in the US sample, the site in Norway recruited an extra 70 children in this age range.

When the longitudinal cohorts and cross-sectional samples for the six sites are combined, the total MGRS sample size is about 8,500 children. The high compliance and low attrition rates that have been experienced ensure that the new growth curves will be based on a sample size that exceeds the minimum required sample of 200 children for each sex and age group.

Information collected and study questionnaires

The study forms were centrally prepared by the WHO Coordinating Centre accompanied by interviewer guides with detailed instructions for training and field use. The questionnaires included closed questions with pre-coded answers. In addition to the data collected on anthropometry and motor development, information was gathered on socioeconomic, demographic, and environmental characteristics; perinatal factors; morbidity; and feeding practices. The anthropometric measurements, described in detail in a separate paper [20], included weight, length, height (in the cross-sectional study only), head and arm circumferences, triceps and subscapular skinfold thicknesses, and parental weight and height. Motor development data covered the acquisition of six milestones: sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone, and walking alone. The motor development protocol is described in detail in a separate paper in this supplement [22].

All questionnaires were kept as short as possible to improve responsiveness and sample retention. Therefore, all candidate questions were scrutinized initially to ensure that they served at least one of the following purposes: establishing eligibility (e.g., socioeconomic status, intention to breastfeed); describing the sample (e.g., demographic and environmental variables); standardizing findings across centers (e.g., parental height); planning breastfeeding support (e.g., initiation of breastfeeding); assessing continued eligibility (e.g., feeding practices, illnesses); guiding future use of references (e.g., vitamin and mineral supplements); or assessing possible selection biases (e.g., maternal work).

A number of different study forms were used in the longitudinal study:

- A screening form, administered at birth, was used to evaluate eligibility and recruit mothers and newborns. It included data on specific exclusion criteria, such as those related to the family's socioeconomic status, the mother's intention to breastfeed, the newborn's gestational age, and maternal smoking behavior.
- A breastfeeding-in-hospital form, which described breastfeeding initiation, timing, and pattern.
- Four breastfeeding-at-home forms were used at weeks 1 and 2 and months 3 and 6. Information was collected on the establishment of lactation, problems experienced in the first two weeks (such as delayed onset of milk production and breast infections), and practices with potentially adverse influences on continued lactation (such as pacifier use and contraception).
- A baseline form administered at the day 14 visit collected information on socioeconomic, demographic, and environmental factors; pregnancy history; and parental anthropometry.
- The follow-up questionnaire was administered at each of 20 follow-up visits to record detailed information on feeding patterns (including the 24-hour dietary recall for the preceding day); maternal and child morbidity; use of vitamin and mineral supplements; maternal employment, smoking, and weight; and child anthropometry.
- For motor development, as many as 14 forms were completed in months 5 to 24, but children who could walk independently before the age of 24 months required the completion of fewer forms. All six milestones were assessed on each occasion.
- An end-of-participation form specifying the reason for ending participation was completed for all subjects who were recruited at the initial screening. Possible reasons included ineligibility or refusal established at the day 14 visit, reasons for dropping out from the study on a later occasion, and the end of follow-up for those who successfully completed the study.
- A 12-month-visit questionnaire was administered to mothers who, although eligible, did not intend to breastfeed; who refused to participate in the study
at any stage; or who dropped out of the study before 12 months for reasons other than child illness. The form gathered selected anthropometric data and information related to the child’s morbidity and feeding history.

The cross-sectional study used three study forms:

» A screening form collected information used to establish eligibility on variables similar to those used in screening for the longitudinal study.

» A survey form covered socioeconomic and demographic factors, child feeding history and morbidity, and parental and child anthropometry.

» In the context of the mixed-longitudinal design, one or two follow-up forms (abbreviated versions of the survey form described above) were used in Brazil and the United States to gather data on anthropometry and child morbidity in the intervals between visits.

Quality control

Rigorous scientific standards have been applied to this complex, multicountry, field-based project. This section summarizes the main measures taken to ensure data quality, most of which are detailed further elsewhere in this supplement [20–22]. Quality control measures included the following:

» Pilot testing of study protocol;

» Use of pretested, standardized data collection forms and detailed interviewer guides;

» Translation into local languages and back-translation of questionnaires and other forms;

» Careful selection, thorough training, and close supervision of staff;

» Regular visits to study sites;

» Training on anthropometric measurements and motor development assessment by international experts with annual site visits by the experts for standardization and/or retraining purposes;

» Regular standardization sessions throughout data collection, with assessment of intra- and interobserver reliability [20, 22];

» Specially designed and highly reliable measuring equipment that was calibrated frequently [20];

» Coordination meetings and staff exchanges among sites;

» Continuous data quality assurance from the point of data collection (independent measurements by two standardized observers [20]), through all stages of data management to their incorporation into the MGRS master files [21];

» Repetition of 10% of all interviews on the telephone;

» Continuous central monitoring of the timing of visits (including delayed, advanced, or missed visits), frequency of repeated measurements, missed measurements, investigation of outliers, terminal digit preference, and results of anthropometric and motor development standardization sessions.

The monitoring of data quality was effective in identifying deviations from MGRS standards, and early, appropriate remedial measures were taken.

Data management and analysis

The MGRS data management system is described in full elsewhere in this supplement [21]. Data were entered concurrently with data collection, verified and validated at the study sites, and sent on a monthly basis to the Coordinating Centre at WHO. MGRS master files were consolidated and ongoing data quality control analyses were carried out at the Coordinating Centre to monitor study implementation and assess adherence to the study protocol.

All data analyses will be conducted at the Coordinating Centre. The Coordinating Centre will be responsible for constructing the new growth references using state-of-the-art statistical techniques. In preparation for the analysis phase, a review of the different methods for the construction of distance, velocity, and conditional growth references was recently conducted by WHO. A full description of the 30 methods reviewed is beyond the scope of this paper. The review document was circulated for external peer review and discussed at a WHO meeting of an ad hoc statistical advisory group. The group identified several criteria for assessing the different methods (e.g., distributional assumptions, curve fitting, age handling, and model simplicity) and, based on these criteria, selected methods to be tested for the growth parameters included in the MGRS. Model diagnostic tools for assessing the appropriateness of the selected methods were also identified. Given the numerous sets of growth reference data that will be produced—including novel references based on circumferences, skinfolds, and growth velocity—the construction and testing of the various references promises to be a complex and challenging task.

Methodological issues

An important concern when proposing a reference based on recommended practices is how such restrictions may affect other characteristics of the reference sample. For example, mothers who choose to breastfeed exclusively or predominantly may also present behaviors other than feeding choices that influence child growth. If a reference population is overly homogeneous, the distribution of values will be too narrow, resulting in statistically based cutoffs that are closer to the mean than would occur in an appropriately heterogeneous reference population.

In response to the concern that the prescriptive approach taken for the development of the new reference might result in an excessive degree of sample selectivity, measures were built into the study protocol.
to minimize bias and assess the potential influence of selection bias on the outcomes of interest:

**Measures to minimize inappropriate sample selectivity**

- Implementation of the study in sites where at least 20% of the mothers in the study subpopulation were likely to comply with the feeding recommendations of the study (tables 1 and 3).
- Application of operational definitions of feeding recommendations that would allow a greater proportion of children to be included in the growth reference data set. Some flexibility in the operational definitions was expected to reduce selectivity problems with the cohorts to be followed and to lessen economic and logistic constraints. Furthermore, available evidence and analyses conducted during development of the MGRS protocol indicated that there were small, if any, differences between the growth of exclusively and predominantly breastfed infants in the first six months of life [8, 27] and that postnatal growth did not appear to be very sensitive to the differential timing of introduction of complementary foods among healthy infants living in safe environments [9, 28]. It was therefore decided that, for the purpose of constructing the growth curves, the feeding criteria to be used would be those listed in table 3. However, at the field level, mothers participating in the MGRS would be advised to breastfeed their infants exclusively for as close as possible to six months, with introduction of complementary foods by the six-month visit.

- Provision of intensive breastfeeding support to participating mothers to enhance compliance and reduce selection bias by ensuring a high level of compliance with feeding recommendations. To allow a high proportion of mothers wishing to breastfeed to actually do so, lactation counseling was made an essential part of the MGRS. At each site, trained counselors visited participating mothers frequently in the first months after delivery to help successful breastfeeding initiation and to advise on subsequent problems. The first visit took place within 24 hours of delivery, and subsequent visits were made at 7, 14, and 30 days, and then monthly thereafter until at least the sixth month. Additional visits were carried out whenever feeding problems occurred. A 24-hour hotline also was made available to mothers for emergency support. Mothers also received advice on complementary foods—with emphasis on energy density, feeding frequency, and micronutrient content—according to locally adapted complementary feeding guidelines. Descriptions of the local lactation counseling teams and complementary feeding guidelines are provided elsewhere in this supplement [14–19]. Compliance with feeding recommendations was monitored centrally throughout the study, and lactation counseling was strengthened as required. Preliminary results strongly suggest that the above measures have been effective and that compliance rates across sites have been high, minimizing concerns about the selectivity of the MGRS sample.

**Measures to assess sample biases**

Two key measures were included in the study protocol to permit the assessment of possible selection biases affecting the sample:

- Follow-up of the entire cohort independent of compliance status. This allows the comparison of the patterns of growth of children whose mothers complied with the feeding and smoking recommendations with those who entered the study but whose mothers subsequently failed to comply with the recommendations of the study.

- The 12-month study. This substudy involved visiting a sample of eligible nonparticipating infants on their first birthdays to compare their attained weights and lengths with those of the cohort children. Four categories of children were included in this substudy: those whose mothers refused to participate at screening; those whose mothers did not intend to follow the feeding recommendations at screening; those excluded at the day 14 visit because the mother had started feeding other milks; and those who dropped out of the study before the age of 12 months.

**Study organization and field logistics**

**Study organization**

The study organization is presented in figure 4. The study was initiated, coordinated, and managed by the Department of Nutrition of WHO, where the MGRS Coordinating Centre was located. The Steering Committee consisted of WHO staff from the Coordinating Centre, the investigator(s) at each participating site, and representatives from the United Nations University and UNICEF. The Steering Committee met four times throughout implementation of the study to review the progress of the study, ensure uniformity of data collection from the different sites, and discuss substan-
tive issues that arose. The study structure included an Executive Committee, formed by five members of the Steering Committee, which reviewed the progress and problems of the study on a regular basis and resolved substantive issues that arose from the implementation of the study. All local adaptations made to the MGRS protocols or issues related to the technical conduct of the study required review and approval by the Executive Committee. The Executive Committee also decided on the selection of study sites, the continuing participation of selected sites, and issues related to the inclusion or exclusion of data in the pooled international data set. An Advisory Group, formed by internationally recognized experts in anthropometry, epidemiology, statistics, nutrition, and human biology, provided technical advice to the Coordinating Centre, Executive Committee, and Steering Committee. Policies related to the dissemination of results and data ownership were developed prior to initiation of the study.

Field logistics

Fieldwork was undertaken by approximately 200 staff members working in different teams covering the areas of coordination, screening, lactation counseling, follow-up, and cross-sectional study. Data management teams were also present in each site. Further information on the study teams and other aspects of field logistics is presented in the papers describing the implementation of the study at specific sites [14–19]. For those interested in replicating the study elsewhere, the Manual of Operations is available on request from the first author.

Ethical issues

The study complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects [29] and received ethical approval from international, national, and local ethical review committees. Written informed consent was obtained from the parents of all children enrolled in the study.

Discussion

Growth references for infants and young children are among the most widely used instruments in public health and clinical medicine. In collaboration with a number of institutions worldwide, WHO has undertaken a major initiative to develop new growth references for infants and young children. The approach taken avoids the limitations imposed by descriptive designs that portray growth characteristics of geographically defined samples that are limited in their definition of health by relying only on the absence of overt disease at the time of measurement. Although the absence of disease remains a requirement in the WHO approach, it is no longer a sufficient criterion. The adopted strategy also requires that the reference population be defined on the basis of a number of other parameters centered on normative behaviors and other characteristics strongly associated with healthy outcomes. Furthermore, it requires that an international sample of children be used.

The MGRS is an ambitious undertaking, but the goals established on initiation of the study have been achieved successfully. The rigor with which the protocol was implemented and the data assurance procedures that were put in place have yielded a data set of outstandingly high quality. Factors that contributed to success were modern communication systems that allowed close and frequent contact between the Coordinating Centre and the sites, the continuous monitoring of data quality, the early detection and adoption of remedial measures for identified problems, and ongoing standardization within and between sites. The path to success, however, was not free of challenges.

Initial important challenges were the selection of study sites and the need to raise funding from external donors. The high cost of the study required funding from multiple donors and was largely responsible for the staggered initiation of the study in the six sites, making its management at times difficult. The high level of collaboration and uniformity that was required by a multicenter, multicultural study of this nature also presented major challenges. Close central monitoring was applied to ensure adherence to study procedures to guarantee the collection of comparable data. During the seven years of data collection, the Coordinating Centre maintained almost daily contact with the local investigators and data managers through modern communication systems and conducted frequent site visits to answer queries and assist in the data collection process. Locally, periodic coordination meetings also were conducted. There were also substantial cross-site staff exchanges to assist in lactation support, data management, data quality assurance, or motor development assessments. This created a sense of international teamwork that contributed significantly to the success of the MGRS.

The development and testing of the various growth references promises to be a complex and challenging task. This expectation is borne out by recent national experiences of a similar nature. The wealth of data being collected will allow not only the replacement of the current international references on attained growth (weight-for-age, length/height-for-age, and weight-for-length/height) but also the development of new references for triceps and subscapular skinfolds, head and arm circumferences, and body mass index. The longitudinal nature of the study will also allow the development of growth velocity curves. Health-care providers will not have to wait until children cross an
attained growth threshold to make the diagnosis of under- or overnutrition, because velocity references will enable the early identification of children in the process of becoming under- or overnourished. Similarly, the documentation of the timing of motor milestones in the longitudinal component will further enhance the value of these data by providing a unique link between physical growth and motor development. The main drawback of the new growth curves, however, is that they will cover only children up to five years of age. The need to expand this effort to older children is evident.

Ahead of us lies the implementation of the new growth references at the country level. In preparation for this phase, we recently conducted a worldwide survey of national practices in the use and interpretation of growth charts that highlighted the interest many countries have in adopting the new growth references when they become available [30]. The results from the survey also indicate that the process of replacing existing growth charts and retraining fieldworkers in the uses and interpretation of new ones must go beyond the simple change of charts, to revisiting growth monitoring practices as a whole. Intensive training efforts at all levels will be required to overcome the difficulties health workers experience with the use and interpretation of growth curves and to disseminate knowledge about effective interventions to prevent or treat either excessive or inadequate growth at both the individual and the population levels. Undoubtedly these future efforts will require a number of partnerships for their successful implementation.

Thirteen years have passed since the seed for this effort was planted. It is reasonable to ask whether the preparatory phases could have been shortened. We think that the long preparatory activities, including several Working Groups and review committees, have been decisive for the successful implementation of the study.

It is unlikely that the high level of uniformity would have been achieved in such a complex multicultural project without this investment of time and effort.

The completion of weight, length, and head circumference references is anticipated before the end of 2005. The remainder of the references should be ready by 2006 (fig. 2). Of particular concern is a smooth global transition to the new references by field testing and/or use simulation of provisional references that take into account the diverse settings in which individual and population assessments occur in both developed and developing countries. This will be accomplished before the growth references are released.

The MGRS will provide a technically sound set of tools for assessing the growth and development of children worldwide for many years to come. An important characteristic of the new reference is that it makes breastfeeding the biological “norm” and establishes the breastfed infant as the normative model. Health policies and public support for breastfeeding will be strengthened when breastfed infants become the reference for normal growth and development. By prescribing the nature of the sample, the recommended approach will provide a single international reference that represents the best description possible of growth for all children less than five years of age and approximates the closest attainable “standard” of physiologic growth.

Full details about the procedures and methods, such as those contained in this supplement, are often not available in the literature. This study will be an important source of information for years to come about child growth and development and infant nutrition. It is therefore important to have a faithful record of the planning, methodology, and implementation, particularly for the benefit of those who may not have been directly involved with the MGRS but will be using the new growth charts in the near future.

References