

Rationale for developing a new international growth reference

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Abstract

The rationale for developing a new international growth reference derived principally from a Working Group on infant growth established by the World Health Organization (WHO) in 1990. It recommended an approach that described how children should grow rather than describing how children grow; that an international sampling frame be used to highlight the similarity in early childhood growth among diverse ethnic groups; that modern analytical methods be exploited; and that links among anthropometric assessments and functional outcomes be included to the fullest possible extent. Upgrading international growth references to resemble standards more closely will assist in monitoring and attaining a wide variety of international goals related to health and other aspects of social equity. In addition to providing scientifically robust tools, a new reference based on a global sample of children whose health needs are met will provide a useful advocacy tool to health-care providers and others with interests in promoting child health.

Key words: Anthropometry, breastfeeding, child health, child nutrition, growth monitoring, growth references, growth standards, human rights

Introduction

Growth references are among the most commonly used and most valuable tools for assessing the general well-being of individuals, groups of children, and the communities in which they live, and for tracking progress in reaching a range of health and other, broader goals related to social equity. The value of growth references resides in the fact that numerous physiological processes must proceed normally and many needs must be met in fetal life and childhood if growth is to proceed normally. Thus, although assessing growth is insufficient as a means of adequately evaluating the health status of an individual or a population, normal physical development is a necessary aim of any strategy that includes aspects of well-being as key outcomes. The marked vulnerability of the health of infants and young children also makes assessments of child growth a “sentinel” indicator in evaluations of the health and socioeconomic development of communities in which they live.

The 1993 WHO Expert Committee on the use and interpretation of anthropometry

Given the importance of normal growth as a summary indicator for health, it is clearly within the set of responsibilities of the World Health Organization (WHO) to establish norms for it. In keeping with this normative function, the WHO has periodically convened Working Groups and Expert Committees to examine issues related to anthropometry. The most recent WHO Expert Committee to review this topic was convened in 1993 [1].

In the past, WHO’s attention to this topic focused principally on the anthropometry of infants and young children [2–4]. The 1993 Expert Committee, however, was asked to address the use and interpretation of anthropometry throughout the life cycle. This broadened interest signaled an increased appreciation of the utility of anthropometric measurements and indicators

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for the screening and evaluation of the health status of individuals and populations of all ages, and the value of changes in anthropometric measurements in the assessment of progress in meeting health, equity, and other societal goals.

WHO organized seven Working Groups in preparation for the 1993 expert consultation to review issues specifically relevant to pregnant and lactating women, the fetus and newborn infant, infants and young children through 2 years of age, children 2 to 10 years of age, adolescents, adults, and the elderly. The Multicentre Growth Reference Study (MGRS) was a direct result of the deliberations of the Working Group on Infant Growth [5].

The WHO Working Group on Infant Growth

The Working Group on Infant Growth was charged with developing recommendations for the appropriate uses and interpretation of anthropometry in infants and young children, i.e., for individuals and populations in diverse operational settings; identifying and/or developing reference data for anthropometric indicators; providing guidelines on their uses; and identifying crucial issues and gaps in knowledge in need of further development. From the beginning of its deliberations, the Working Group focused on incongruities presented by the apparent poor growth of healthy breastfed infants of well-nourished women living in favorable environments. This apparent poor growth was inconsistent with the multiple health benefits associated with breastfeeding and other health behaviors associated with these demographic groups and the environments in which they resided. These inconsistencies focused the Working Group's attention on an evaluation of the current international reference, the US National Center for Health Statistics (NCHS)/WHO International Growth Reference [6], and on a systematic review of the growth performance of breastfed infants studied under relatively highly controlled conditions.

Brief history of the current international reference

The history of the current international growth reference was reviewed in 1996 by de Onis and Yip [7]. This reference was based on a framework initially recommended by the Food and Nutrition Board of the United States National Academy of Sciences [8, 9] and implemented by a joint NCHS and Centers for Disease Control task force [6, 10]. The task force compiled longitudinal data (0 to 23 months) collected by the Ohio Fels Research Institute from various groups of children studied before 1975 and cross-sectional data collected by the US Health Examination Surveys conducted from

1960 to 1975 in children 2 to 18 years of age. The Fels data were collected from predominantly formula-fed infants who resided in a restricted geographic area and were of relatively high socioeconomic backgrounds. The US Health Examination Surveys were designed to reflect representative samples of US children.

During the same period, WHO convened an expert group in 1975 to advise it on the use of anthropometric indicators in nutrition surveys and surveillance activities [11]. This group recommended the use of reference data for these purposes and outlined specific criteria that such data should meet. Although none of the growth data available at that time met the recommended criteria, the NCHS data were recommended by this group for use as the international reference [12]. The major limitations of the infant portion of these data and the reference constructed from them were that the sample was limited to infants of European descent residing in the United States, measurements were taken only every three months, and the analytical methods available at the time were inadequate for the task and were likely to inappropriately depict the pattern and variability of normal growth [7]. The latter two shortcomings contributed to a mischaracterization of the shape of the growth curve, particularly during the first six months when rapid growth occurs, and whose accurate characterization is crucial for effective lactation management.

Summary of the analyses of the Working Group

To review the growth performance of healthy breastfed infants, the Working Group assembled published and unpublished growth data from infants who were exclusively or predominantly breastfed to at least 4 months and who continued breastfeeding for the first 12 months. The Working Group applied fairly conservative criteria to data selection to maximize the likelihood that the growth pattern of the selected sample was not constrained by environmental factors, the nutritional status of the mother, the index pregnancy, or inadequate lactation support. A sample of 226 infants (109 boys and 117 girls) who met the feeding and other criteria outlined above was selected from the larger set of published and unpublished data available to the Working Group. Although this sample had a broader geographic base than the Fels sample, the "pooled breastfed data set" was also from children predominantly of European background and of relatively high socioeconomic status. Additional details of these analyses have been published elsewhere [5, 13].

Among the more salient findings from these analyses are three results particularly relevant to this discussion. First, it was clear that the growth of this conservatively

selected sample of infants deviated negatively from the current international reference and that the magnitude of the deviation was sufficiently large to interfere with nutritional management. The mean Z scores for length-for-age, weight-for-age, and weight-for-length of children 1 to 12 months of age, calculated on the basis of the current international reference, are summarized in figure 1. Rather than the anticipated approximate tracking of early growth trajectories, weight-for-age Z scores fell progressively from months 2 through 12, Z scores for weight-for-length showed a similar pattern, and those for length-for-age fell through 8 months.

To further evaluate the patterns of growth represented by the current international reference and the pooled breastfed data set, the Working Group examined a data set from a WHO Human Reproduction Programme (HRP) study conducted in five countries: Chile, Egypt, Hungary, Kenya, and Thailand [14]. The HRP data set included 1,273 infants whose geographic origins and socioeconomic status were more diverse than those of infants who comprised either the current international reference or the pooled breastfed data set. The Working Group compared the growth of a subset ($n = 382$) of those infants—those who were either exclusively or predominantly breastfed for various lengths of time through the first year—with both the current international reference and the Working Group's pooled breastfed data set.

The results of the weight-for-age comparison are summarized in figure 2. The Z scores of healthy HRP infants fell from approximately month 3 to months 11 or 12 when the basis for comparison was the current international growth reference, or were sustained or slightly increased when the pooled breastfed data set was used as the reference. The HRP group's declining Z scores relative to the current international reference and its sustained tracking of early Z scores relative to the pooled breastfed data set supported the view that the present international reference was inappropriate for assessing the growth of healthy infants, at least through 12 months of age, and that the growth pattern followed by the pooled breastfed data probably

reflected "physiological growth" more closely than did the current international reference.

The third finding was that the variability of growth in the pooled breastfed data set appeared to be significantly smaller than that of the present international reference. These differences were sustained throughout the first 12 months for length and weight in both males and females. The consequences of the decreased variability are illustrated in figure 3. As is evident from this figure, narrowing the distance between the means and the commonly used statistical cutoffs (± 2 SD) to identify children at significant risk for either inadequate or excessive growth significantly influences the classification of individual children into either category and estimates of the prevalence of either condition. The narrower variation in the pooled breastfed data set may have resulted from its conservative selection criteria. Alternatively, the wider variation depicted by the current international growth reference may reflect the apparently broad definition of health used to select the Fels population, i.e., the absence of observable illness and the lack of feeding criteria in selecting the study sample. Artificial milks used at the time the Fels data were collected are no longer available, as manufacturers have improved infant formulas steadily. Thus, wider growth variability may have resulted from responses to "nonoptimal" formulas that subsequently were replaced by others that presumably were improved based upon new knowledge of nutritional needs during infancy.

Conclusions of the Working Group

The Working Group's interpretation of these and other related findings outlined in its report to WHO [5] led it to conclude that new references were necessary and that it was time to consider the production of references that would more closely approximate standards, i.e., to describe how children *should* grow in all settings rather than to limit oneself to a description of *how* children grow in a specific setting and time.

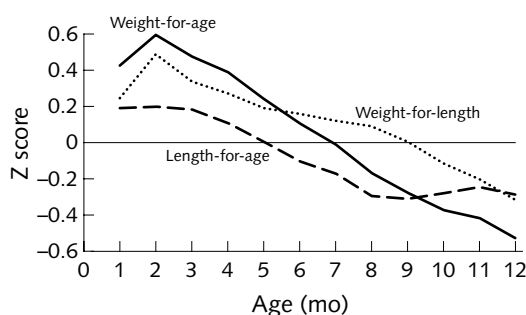


FIG. 1. Mean Z scores of infants in the "pooled breastfed data set" relative to the NCHS/WHO international reference [5]

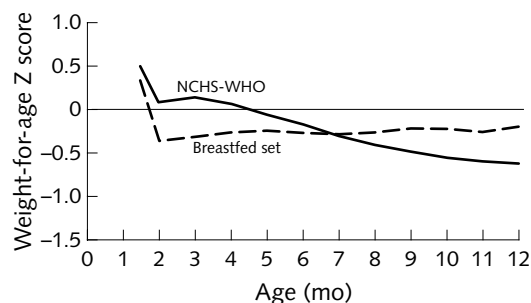


FIG. 2. Mean weight-for-age Z scores of infants enrolled in the WHO Human Reproduction Programme study compared with the NCHS/WHO international reference and the "pooled breastfed data set" [5]

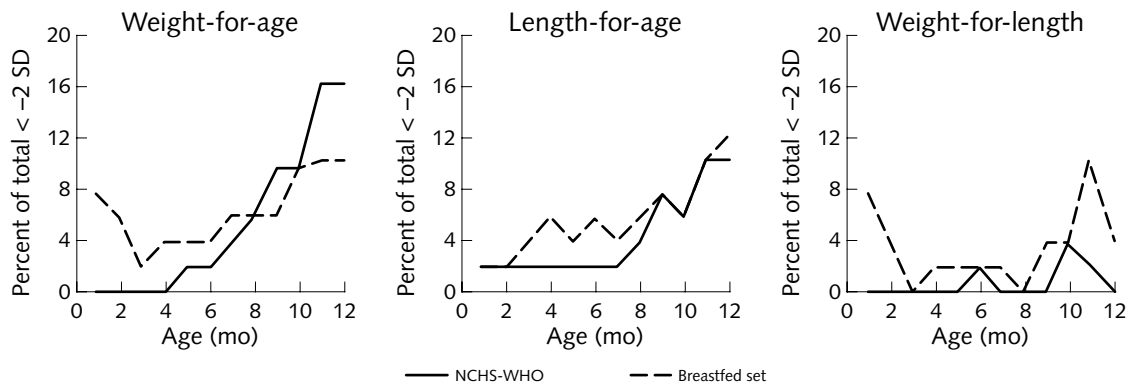


FIG. 3a. Percentages of peri-urban Peruvian infants with weight-for-age, length-for-age, or weight-for-length below the -2 Z score cutoff, according to the NCHS/WHO international reference and the “pooled breastfed data set” [5]

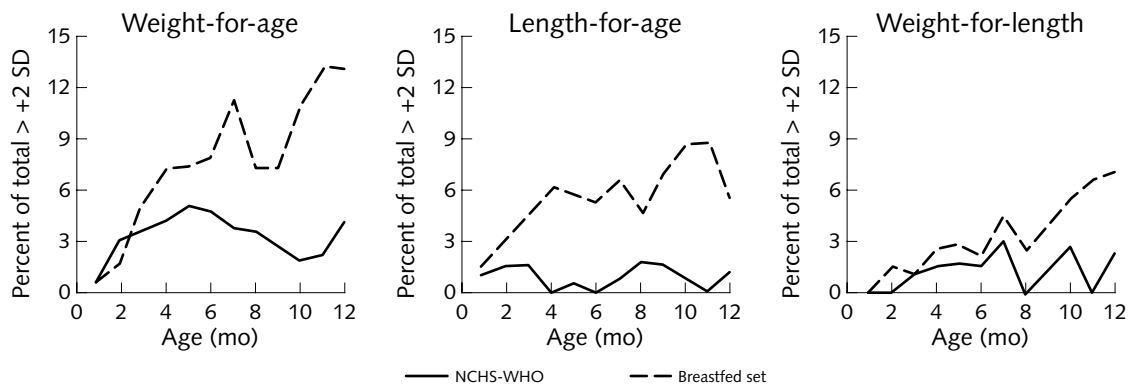


FIG. 3b. Percentages of US and European formula-fed infants with weight-for-age, length-for-age, or weight-for-length above the $+2$ Z score cutoff, according to the NCHS/WHO international reference and the “pooled breastfed data set” [5]

Three principal lines of thought led to this conclusion. First, the group surmised that at least one key biological assumption inherent in the present international reference is flawed, namely, that infant growth is probably not independent of feeding choices (at least not under conditions that characterized infant feeding choices when the present international reference data were collected). Knowledge of the nutritional, immunological, and reproductive benefits of breastfeeding argues strongly for the breastfed infant as the standard for physiologic growth. The narrower variability estimates derived from the pooled breastfed data set may reflect these biological advantages. The narrow ethnic representation of the pooled breastfed data set is an unsatisfactory explanation for the decreased variability, because of the similarities between the Fels data and the breastfed pooled data set in this regard.

Second, the group recommended that early growth patterns be documented in increments shorter than three months. One possible partial explanation for the deviations between the current international reference and the growth pattern of breastfed infants is that measurements at three-monthly intervals are inadequate to capture the dynamic pattern of growth

in the first six months. An accurate depiction of those patterns was viewed as especially important because of the role that growth monitoring plays in lactation management during this period.

Third, the Working Group concluded that limitations inherent to curve-fitting or smoothing techniques available at the time of construction of the present international reference may be an additional explanation for the observed growth discrepancies. Advances in analytical capabilities and approaches have made methods applied to construct the present international reference outmoded.

In response to these findings and recommendations, WHO convened a group in 1995 to develop a protocol for the development of new growth references. Because of the nature of public health programs, WHO asked this second Working Group to consider the inclusion of children through the age of five years.

Ancillary analyses

The deliberations of this second Working Group led to additional analyses that were key to the subsequent

design of the MGRS protocol. The rationale for basing a new reference on breastfed infants was clear and reaffirmed by this group; however, the possibility that other health-related behaviors significantly influenced physiologic growth responses was raised in its discussions. Among the issues of most concern were the timing and nature of complementary feeding, the role of nutrient supplements, and selected parental behaviors, most notably smoking and the use of alcohol and other drugs, and the potential for different growth patterns among breastfed infants of diverse ethnicity. Data from a second HRP data set were used [15, 16] to assess each of these issues.

The results of some of these analyses were published subsequent to their availability for planning the MGRS. Growth patterns of breastfed infants from seven countries (Australia, Chile, China, Guatemala, India, Nigeria, and Sweden) were published in 2000 [17]. Multilevel modeling was used to assess between-site growth differences after adjustments for maternal stature and infant feeding pattern. Approximately 120 infants per site were used for these analyses. Although the study was not restricted to socioeconomically advantaged groups, all women who participated were literate and had educational levels well above the average of their countries of residence. Growth patterns were strikingly similar in all countries except China and India. Maternal education was related to infant growth only in India. All sites were urban except for China. Compared with the arbitrarily selected reference group (Australia), Chinese infants were approximately 3% shorter and Indian infants were approximately 15% lighter at 12 months of age. These analyses demonstrated that breastfed infants from economically privileged families (relative to national norms) were very similar despite the wide ethnic differences and diverse geographic characteristics in this second HRP data set. The findings also underscore the utility of the surveys that were undertaken as a prerequisite to the selection of participating sites. This feature of the MGRS is discussed elsewhere in this supplement [18].

The HRP study was also used to assess associations among growth patterns and different durations of exclusive breastfeeding and the types and frequency of complementary foods introduced between four and six months [19]. Small, statistically significant differences in growth were noted among breastfed infants to whom complementary foods were introduced at different times during that interval; however, the magnitudes of those differences were sufficiently small to be biologically unimportant. The most extreme differences were equivalent to approximately 10 centiles of the weight and height distributions at six months of age. These results provided no compelling evidence of benefit or risk from the timing of complementary feeding between four and six months nor from the frequency or types of complementary foods used during

this period by these relatively privileged groups with no major economic constraints and with low rates of infectious illnesses.

In a separate unpublished analysis (report available on request), also based on the second HRP study, associations between the maternal use of alcohol and vitamin or mineral supplements and postnatal infant growth were examined. Alcohol use was examined in the HRP data obtained from Australia, Chile, China, and Sweden. In none of those sites was prenatal or postnatal alcohol use related to postnatal length or weight. The effect of maternal vitamin or mineral supplements was evaluated in the HRP data collected in Australia, Chile, and Sweden. Prenatal or postnatal maternal supplement use was also unrelated to postnatal length or weight in any of those sites.

Maternal use of tobacco was evaluated from the published literature. The second Working Group considered that the effects of smoking on fetal growth [20] and on lactation performance and infant growth [21–23] were important enough to justify inclusion of maternal smoking as an eligibility criterion in the MGRS protocol [18].

Rationale for the MGRS

These analyses, the deliberations of the Working Groups, and extensive peer reviews of the conclusions and recommendations of both Working Groups culminated in the development of a study protocol and operational framework with four salient features: (a) a clearly “prescriptive” approach that included the consideration of infant feeding choices, maternal support for breastfeeding, maternal smoking, and environmental conditions that supported unconstrained physiologic growth; (b) an international sampling frame; (c) heavy reliance on current information technology and its increasing accessibility to document fully the planning and implementation phases of the study, to implement a level of rigor in data management and quality control commensurate with the construction of biological references or standards, and to avoid constraints on the study’s selection of analytical methods for curve construction (following a systematic review of contemporary approaches for the analysis of longitudinal and cross-sectional data); and (d) a proposed link between anthropometric assessments and specific functional outcomes of predictive relevance to the well-being of children. This proposed link led to the subsequent addition of the motor development component of the study, which is also described in this supplement [24].

By adopting a “prescriptive” approach, the protocol’s design went beyond an update of how children in presumably healthy populations grow at a specific time and place. The MGRS was designed to provide data

that describe “how children *should* grow” by including in the selection criteria of the study specific behaviors that are consistent with current health promotion recommendations (e.g., breastfeeding norms, standard pediatric care, and nonsmoking requirements). Thus, the implemented design advanced beyond the construction of a device for grouping and analyzing data (a *reference*) for the purpose of enabling value-free comparisons, to the explicit recognition of the need for *standards* (or as close to them as possible), i.e., devices that enable value judgments by incorporating norms or targets in their construction.

By including an international sampling frame, the design recognizes the solid evidence that all children grow very similarly for the first five years of life when their physiologic needs are met and their environments support healthy development; nearly all interethnic variability is probably a result of environmental assaults [1, 25–27]. The development of a reference composed of children from all major global regions (in contrast to the present international reference, which is based on children from a single country, the United States) is also likely to be more acceptable for international use. Moreover, it will detract from the perceived need by some to develop country-specific growth norms based on multiple, often inappropriate methods that lead to difficulties in cross-country comparisons and are likely to contribute to faulty national policies. Arguably, the current obesity epidemic in the United States would have been detectable earlier if a prescriptive international reference had been available 20 years ago. An added feature of the design’s combined prescriptive and international aspects is the strengthening of advocacy for child health.

Key criteria of reliably robust standards and references are their reproducibility and accessibility to evaluation. Extensive documentation of all stages of development and implementation is indispensable to achieve these characteristics. Among the most important goals of the proposed standards is to remain relevant for as long as possible. This requires that design, implementation, and methodological aspects of sampling strategies, measurements, data management, and analyses be documented as fully as possible. Achieving high standards in the MGRS protocol for each of these features—some of which are reviewed in depth in this supplement [28, 29]—was a key aim. Advances in, and the growing accessibility of, information technology made the task easier to achieve than in the past. The rationale for insisting that these aspects be given scrupulous attention is strengthened by the certainty that knowledge is increasing regarding the functional consequences of early growth patterns and the health behaviors that enable them [30, 31]. Thus, the relevance of MGRS-derived instruments as standards should be amenable to evaluation for the foreseeable future.

Although, as recognized previously, normal growth

is necessary to health, it is not sufficient. Interest in growth assessments stems largely from their value as screening tools that signal nonspecific problems when growth is abnormal, or a relative degree of assurance that key physical and emotional needs are being met when growth proceeds as expected. Thus, although normal growth is a necessary enabler of the full complement of functional capacities associated with health, it alone does not assure their attainment. Other resources and conditions, such as educational and physical stimulation within the home, must be accessible to ensure that broader developmental milestones are achieved. This was the basic rationale for the inclusion of motor development assessments in the MGRS. Their broad predictive value and the relative ease with which key motor milestones could be documented in a wide array of field settings supported their inclusion [24]. Linking them closely to anthropometric standards also is expected to be of significant educational value to parents and health-care providers. From a policy perspective, their inclusion is intended to focus attention on growth and broader functional capacities in childhood that are key to normal development in subsequent life stages.

Anticipated results

The MGRS is therefore expected to yield scientifically more robust tools for assessing child growth than are available currently, to strengthen the use of these tools for purposes of child health advocacy, and, because of specific design characteristics discussed in this supplement [18], to provide a wider array of references for expanded uses, e.g., much more appropriate tools for the successful management of early lactation and the monitoring of childhood overweight and obesity.

The current international reference is limited to “attained” measures. This limits the interpretation of anthropometric changes and generally restricts the diagnosis of under- or overnutrition to values that cross a preselected cutoff point assumed to reflect a level of risk for restricted or excessive growth, e.g., the 3rd or 97th centiles, respectively. These are generally interpreted to reflect a level of risk that triggers further evaluation, since only 3% of the target population is expected to be above or below either cutoff; however, for reasons reviewed briefly above, the bases of “value” judgments inherent in such evaluations are problematic, given the “nonprescriptive” nature of sampling schemes upon which the current international reference is based.

International references are currently available only for attained weight-for-age, length/height-for-age, and weight-for-length/height. The MGRS protocol was designed to approximate standards for these and several other attained anthropometric measurements: body mass index (BMI)-for-age, mid-upper-arm

circumference (MUAC)-for-age, head circumference-for-age, subscapular skinfold-for-age, and triceps skinfold-for-age. Additionally, velocity references should be available for a number of growth parameters because of the longitudinal component of the MGRS [18]. Velocity references will most likely be valuable in the early assessment of the risk of overweight in infancy and thus contribute to the early management of this increasingly prevalent and worrisome public health problem. Rather than limiting risk designations to after either state has very likely been achieved, velocity references should enable the identification of children at risk of becoming underweight or overweight. This expanded set of tools is expected to enhance the use and interpretation of anthropometric references, as set out in the 1995 Report of the WHO Expert Committee on this topic [1].

The “prescriptive” sampling scheme described above is also expected to provide improved estimates of the variability of normal growth. These improved estimates should make risk assessments more robust at both the individual and the population levels. If the qualitative differences in variability between the present international reference and the pooled breastfed data set summarized in figure 3 are confirmed by the MGRS, estimates of under- and overnutrition will be impacted, but it is difficult to estimate this quantitatively until analyses of MGRS data are complete.

The selection of breastfed infants as the foundation of new standards also contributes significantly to advocacy in support of current international infant feeding policies [32, 33] and will be much more supportive of lactation management protocols than is the current international reference. The lack of congruence between the feeding histories of infants who contributed to the current international reference and international feeding recommendations unnecessarily sent inconsistent, and potentially confusing, messages. Identifying the breastfed infant as the standard aligns policy with health screening evaluations and potentially provides a goal for manufacturers of infant formula to attain and for national and international regulators to consider in approval processes as new formulations are brought to market.

Broadening the definition of “health” beyond the absence of overt disease to include recommended feeding practices and other health behaviors (e.g., criteria related to maternal smoking behaviors) and selecting infants from populations likely to receive recommended pediatric care should enhance expectations that standards of care and recommended family health-care practices will be accessible to all infants and young children. Tethering such behaviors to the most frequently used health screening tool is thus expected to “raise the bar” substantially in terms of international expectations regarding infant and young child care.

Significance of anticipated results

Upgrading international growth references to tools that more closely resemble standards has substantial significance for other widely accepted international goals. They are expected to make significant contributions to meeting the UN Millennium Development Goals (MDGs) by directly strengthening the framework necessary to achieve them, especially because these new tools are consistent with the human rights approach at the core of the MDGs. The tools will play direct roles at the national, regional, and international levels in monitoring progress toward meeting four of the seven MDGs and, less directly, the remaining three [34]. Although these goals represent a political consensus, and some may question their long-term relevance, the basic aspirations they embody will most likely remain at the core of efforts to narrow social, economic, and health disparities.

Clearly, MDGs such as the eradication of extreme poverty and hunger, achievement of universal primary education, promotion of gender equality and empowerment of women, and reduction in child mortality will each be reflected in improved child well-being. Conversely, improvements in those broad goals will be unattainable unless needs that support normal physical growth are met. Progress in meeting infant and child growth standards will depend significantly on improving maternal health, and so it is likely that these standards also will contribute to the fifth MDG. Similarly, progress in meeting the growth standards will be impossible if we do not succeed in combating HIV/AIDS, malaria, and other diseases, the sixth MDG. Achieving physiologic growth in young children also is linked inextricably to many of the specific aims that comprise the more general MDGs, e.g., ensuring environmental sustainability.

Finally, it is of seminal importance to recognize the basic role that the UN Human Rights Treaty System plays in motivating international aspirations in health and other sectors. The relevance of the MDGs is fully appreciable only within the context of that treaty system. Among the six pillars of the system is the Convention on the Rights of the Child (in force since September 2, 1990).^{*} This convention recognizes duties and obligations to children that cannot be met without attention to normal human development. The use of a growth standard derived from a worldwide sample of children and based on the biological reality that environmental differences rather than genetic endowments are the principal determinants of disparities in physical growth is an important first step in carrying forward our duties and obligations to the human family.

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*The six treaties that comprise this system are the Convention on the Elimination of All Forms of Racial Discrimination (in force since January 4, 1969); the International Covenant on Civil and Political Rights (in force since March 23, 1976); the International Covenant on Economic, Social, and Cultural Rights (in force since March 23, 1976); the Convention on the Elimination of Discrimination Against Women (in force since September 3, 1981); the Convention Against Torture (in force since June 26, 1987); and the Convention on the Rights of the Child (in force since September 2, 1990).

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