PERSPECTIVES IN HUMAN GROWTH, DEVELOPMENT AND MATURATION

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CHAPTER 4

A NEW INTERNATIONAL GROWTH REFERENCE FOR YOUNG CHILDREN

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1. INTRODUCTION

Anthropometric references for infants and young children are among the most used tools for assessing paediatric well-being. At the population level growth references are useful for predicting general emergencies related to food and nutrition, assessing the equity of distribution of economic resources within and between communities, evaluating the suitability of general weaning practices, and for screening and following at-risk groups. For individuals, growth references are the mainstay to growth monitoring and promotion, help identify the optimal timing of the introduction of complementary foods, often are used to assess maternal lactation performance, are applied in the detection of growth faltering, and help in the diagnosis of failure to thrive and excessive growth.

Recently, several concerns were raised regarding the adequacy of currently existing growth references, particularly that developed by the National Center for Health Statistics (NCHS) and currently supported by the World Health Organisation (WHO 1995a). The NCHS data for the first two years of life originated from a single, ethnically homogeneous North American community where most babies were artificially fed, while recent research shows that babies following current feeding recommendations show different growth trajectories (WHO 1995b) while presenting excellent health status. Additional concerns with the NCHS-WHO curves were that measurements were taken at wide intervals and that curve-fitting procedures were outdated. In 1995, the WHO Expert Committee on "Physical Status: the use and interpretation of anthropometry" recommended the replacement of the NCHS-WHO reference data with a new international growth reference. The main conclusions of the Expert Committee have been summarised in an earlier publication (de Onis and Habicht 1996).

P. Dasgupta and R. Hauspie (eds.), Perspectives in Human Growth, Development and Maturation, 45–53.

A WHO Working Group was assembled to develop the protocol for the n study, which is aimed at building a new international growth reference for asses the growth status of populations and of individual children. The present cha summarises the main features of this new study. The full protocol (WHO 199 available from the authors on request.

The new reference is intended for assessing the growth of singleton chil under five years of age, throughout the world. Its basic assumption is that inf following current feeding recommendations are growing optimally. The curves n therefore be considered as prescriptive (or optimal) standards, as opposed traditional normative (or descriptive) standards based on samples of child regardless of feeding or other behaviours.

A major concern when proposing a reference based on recommended practic how such restrictions may affect other characteristics of the sample. The common the recommended practices are in the society where the reference data being collected, the more it is likely that other, possibly unmeasurable selec forces will also be operating. If a reference population is highly homogeneous, distribution of values will be unacceptably narrow, resulting in cut-off values cl to the mean than would occur given an appropriately heterogeneous refer population. Measures to avoid the selectivity problem will be further addre below.

The new curves are aimed at both population and individual uses. Popula uses will include providing a reference for comparing groups of children, eith terms of means (or medians) or of the proportions of children below or above a g cut-off point. Individual uses include screening for attained size (weight, length, on a single occasion, and monitoring growth over time.

2. STUDY DESIGN

The WHO Multicentre Growth Reference Study (MGRS) will include a longitu study from birth to 24 months of age and a cross-sectional study of children age to 71 months. In the longitudinal study, cohorts of new-borns will be followe for the first two years of their lives, with frequent assessments of feeding prac and growth. It will also allow the assessment of self-selection bias (see below) provide incremental measurements. Children will be identified at birth and visit weeks 2, 4, 6, 8 and then monthly until their first birthday. In the second y bimonthly measurements will be taken.

After two years of age, growth is considerably more linear than earlier, feeding patterns appear to be no longer critical for growth curve constructio cross-sectional design will therefore be adopted for children aged 18 to 71 mo to avoid the time and cost of carrying a longitudinal study in that age range. U 18 months as the lower age limit for this group will allow an overlap betwee two studies. Although the curves will be built for children aged up to 59 mont is necessary to extend data collection to 71 months in order to obtain reli estimates of growth at the end of the fifth year of life (see Sample Size section).

3. POPULATION SAMPLES

There will be different sets of eligibility criteria for subpopulations and for individual children.

3.1 Eligibility of study subpopulations:

The following characteristics will be used for selecting potential study sites:

- *Socio-economic status that does not constrain growth.* This restriction will ensure that the curves reflect the true growth potential of children, not being constrained by factors related to maternal nutrition, to the quality of complementary foods, nor to other social or environmental restrictions.
- *Low altitude.* Centres located at an altitude above 1,500 m will not be included.
- *Low mobility of the target population.* The need to follow up children prospectively for two years renders populations with high migration rates inappropriate. Ideally, previous studies carried out in the area will show that it is possible to follow up at least 80% of families with children for a 12-month period.
- *Minimum of 20% of mothers willing and able to follow feeding recommendations.* This refers to the issue of selectivity. Ideally, investigators should be able to demonstrate that 20% of eligible mothers already follow the recommendations. If this cannot be demonstrated, investigators should satisfy the Steering Committee that this goal is likely to be achieved during the actual study.
- *Existence of breast feeding support system.* Breast feeding support will ensure lower selectivity by allowing a large proportion of mothers willing to breastfeed to actually do so.
- *Local presence of collaborative institutions.* Data collection requires expertise in both epidemiology - particularly in longitudinal studies - and anthropometry. In addition, adequate knowledge of the local epidemiology of breast feeding and of growth deficits is essential for selecting children for the study and for understanding selection pressures.

It is not necessary for the whole population from the study area to have the above characteristics, since these restrictions would probably preclude the participation of any centre outside developed countries. These characteristics, however, should be present among the subpopulation from which study participants will be drawn. For example, the upper classes (and possibly part of the middle classes) would qualify in a less developed country, while most of the population would qualify in a developed setting. Since both the longitudinal and cross-sectional studies will be carried out in the same sites, the subpopulation eligibility criteria apply to both.

The mean birth weight in the target population was not included as an eligibility criterion. However, this was taken into account when selecting sites, in order to ensure a spread of mean birth weights across centres.

3.2 Eligibility of individuals:

Within each selected site, the following characteristics will be applied for selecting new-borns:

- *No health, environmental or economic constraints on growth.* The issue economic and environmental liabilities has been discussed above. Local crite will be used in each site to define adequate socio-economic status. In additi children should not have any illnesses affecting growth.
- *Mother willing to follow feeding recommendations.* Mothers willing to com with current feeding recommendations (see below).
- *Term birth.* Gestational age at birth between 37 and 42 full weeks.
- *Single birth.*
- *Maternal smoking.* Since smoking can affect both lactation performance and inf growth (Meyer 1979; Vio, Salazar and Infante 1991; Mansbach, Greenbaum Sulkes 1991), as well as birth weight (Kramer 1987), mothers who smoked eit before or after delivery are excluded from the study.

Low birth weight babies born at term are not excluded from the sample. T restriction would artificially distort the lower centiles of the curve in the e months.

4. COMPLIANCE WITH FEEDING RECOMMENDATIONS

The study takes the breast-fed infant as the biological "norm". Given that st adherence to the current feeding recommendations might cause important selecti problems with the cohort to be followed, and also due to economic and logi considerations, the following operational criteria are applied in the study:

- Exclusive or predominant breast feeding for at least four months (120 days);
- Introduction of complementary foods by the age of six months (180 days) and
- Partial breast feeding to be continued for at least 12 months (365 days).

To increase compliance, lactation counselling is an essential part of the study each site, trained counsellors visit all participating mothers frequently in the f months after delivery, to help successful breast feeding initiation and to advise eventual problems. The first visit takes place within 24 hours from delivery, subsequent visits at 7, 14 and 30 days, and monthly thereafter until at least the s month. Additional visits are carried out if required. A 24-hour hotline is m available to mothers, for emergency support.

The restriction of the study to subpopulations with a high socio-economic st and no evidence of growth retardation suggests that complementary foods wil generally adequate. Nevertheless, the lactation counsellors also advises mothers complementary foods with emphasis on energy density, feeding frequency and mi nutrient content. Compliance will be assessed by the types of foods given to e individual child. Food frequency data are collected at all visits. In particular, volumes of non-breast milk fluids given and the use of vitamin/mineral supplem are being assessed.

In addition to compliance with feeding recommendations, the following crit are applied for excluding mother-infant pairs from the growth-curve set of longitudinal study:

- *Serious illness.* Children developing a serious illness leading to substar growth faltering will be excluded from the growth-curve set of the study.
- *Age limit.* Children will be discontinued from the longitudinal study when t complete two years of age.

- *Voluntary exclusion.* At any time, mothers not willing to comply with the visit schedule may leave the study. The reasons for the refusal will be recorded

Children who are excluded from the growth-curve set of the study, due to lack of compliance or serious illness, are continue to be visited as scheduled, so that information will be available on their growth. Mothers who refuse to continue are being asked if they would allow one more visit on the next birthday of the child. These visits will allow to document how the growth of children who remain in the study may differ from the growth of other children in the target subpopulation.

5. ANTHROPOMETRIC MEASUREMENTS

Anthropometric measurements taken in the longitudinal study include weight, crown-heel length and head circumference, arm circumference, and triceps and subscapular skinfold thicknesses. The timing for these measurements is described in Table 1. More frequent data collection takes place during the first year — when growth velocity is greater — with a total of 21 visits per child, including the first visit within the first 24 hours of life.

Table 1. Time schedule for the collection of anthropometric measurements in the longitudinal study.

Measurement	*Time frame*	*Frequency*	*No. of visits*
Weight, length, head circumference	Birth	Once	1
	Weeks 2-8	Biweekly	4
	3-12 months	Monthly	10
	14-24 months	Bimonthly	6
Arm circumference, skinfold thicknesses	3-12 months	Monthly	10
	14-24 months	Bimonthly	6

In the longitudinal study, measurements are obtained with a maximum delay of 10% of the child's age (e.g., three days at one month, or 18 days at six months). In the cross-sectional study, children aged 18-71 months have their weight, standing height, head and arm circumference, and triceps and subscapular skinfolds measured once. In addition, children aged 18-35 full months also have their supine length measured. This will allow the precise estimation of the length/height disjunction. It is envisaged that the final curve will have a clear disjunction at 24 months to warn the health worker to move from length to height, thus avoiding some of the problems observed with the NCHS-WHO reference.

The anthropometric instruments and techniques used in all centres are standardised, i.e., similar equipment and measuring procedures are used by all study teams. Children are weighed with the Uniscale (UNICEF, Copenhagen), an electronic scale with precision of 100g that obtains the child's weight by subtraction, by weighing first the mother and then the mother holding the child.

Length is measured with Harpenden Infantometers with digit counter readings 1 mm. The Harpenden Portable Stadiometer with digit counter reading is bei used for measuring both parental and children's height. Circumferences are measur with a flat metal tape 0.7 cm wide calibrated to 1 mm. For skinfolds, the Holta Tanner/Whitehouse calliper is being used (jaw face area: 35 mm^2; pressure betwe the jaws: 10±2 g/mm^2). All equipment is calibrated daily.

Teams are standardised by an international anthropometry expert who vis every participating site prior to the beginning of data collection to train all fie workers. In addition, the international expert visits every site annually. Every tv months, a standardisation session is held in each study site, in which 10 childr are measured twice by each observer, for all measurements. The purpose of t bimonthly standardisation is to ensure the observers are not departing from t recommended techniques, monitor their reliability, and to take corrective measures required. Observers showing inadequate intra- or inter-observer agreement a retrained. This also allows reliability statistics to be monitored within and betwe study sites.

During the study, every anthropometric measure is carried out twice, once each of a pair of observers, who record their results independently. Each set of tv measures is then compared, and if the difference exceeds the maximum allow difference, both measurements are repeated until the measurements are within t allowable difference. If there is no agreement after three sets of duplic measurements, the process is stopped and the last measurements are recorded.

6. QUESTIONNAIRES, DATA MANAGEMENT AND QUALITY CONTRO

All questionnaires include closed questions with pre-coded answers when applicab Questionnaires are centrally prepared in English and translated to the lo languages. These versions are then back-translated into English for comparison w the original forms, and any discrepancies corrected. Detailed interviewers' guic with guidance on all questions are prepared for training and field use.

Data entry takes place simultaneously with data collection at each study site. standardise data entry, centrally-prepared data entry routines automatically carry c range and consistency checks for immediate correction. All records are entered tw for validation purposes. Data being collected is transferred monthly to the c ordinating centre, located in the Department of Nutrition of WHO, where furt quality control analyses take place and compliance with the study protocol assessed.

The main measures to ensure data quality control include:

- Use of pre-tested, standardised data collection forms and detailed intervie guides
- Translation into local languages and back-translation of questionnaires and ot forms
- Careful selection and evaluation of interviewers
- Thorough training course on interviewing techniques
- Training workshop on data management
- Training on anthropometric measurements by a single expert in all sites, follow by initial standardisation sessions with assessment of intra- and inter-obser variability

- Frequent calibration of measuring equipment
- Bimonthly standardisation sessions throughout the data collection period
- Repetition of 5-10% of all interviews
- Simultaneous data entry with centrally-prepared range/consistency checks

7. SAMPLE SIZE

The precision of growth chart centiles is determined by several factors, of which the most important is sample size. Other factors are also relevant, including study design (cross-sectional versus longitudinal), the timing of measurements, and the method of curve-fitting. Many criteria can be used to set the sample size, but four were considered in the present study. These were a) the precision of a given centile at a particular age, b) the precision of the slope of the median curve over a given age range, c) the precision of the median curve overall and the influence of data at particular ages, and d) the precision of the correlation between measurements in the same subjects at different ages. The latter criterion is relevant for velocity references.

Sample sizes were calculated for each of these four criteria, and it was found that a sample size of 200 for the longitudinal study and 200 per 3 months for the cross-sectional study should provide adequate precision. These are the numbers for each sex, and are to be obtained by combining data from several sites.

A relevant finding of the sample size calculations was that the first few measurements, particularly birth weight, have high variance, while between 1 and 4 years this 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 curve at the extremes, birth weight needs to be over-sampled and the upper age limit raised. A four-times larger sample at birth and an upper limit of 71 full months for the cross-sectional study will considerably improve the precision of the curve throughout the whole age range of interest.

To obtain 400 children of both sexes, given six participating sites, 70 children will have to fulfil all criteria in each centre. The number of infants to be initially recruited will depend on the proportions expected to remain eligible (i.e., complying with feeding recommendations, healthy and willing to participate) until the age of two years. For example, if a completion rate of 30% is envisaged, then 233 infants are to be recruited at birth (233 x 0.3 = 70). As a working figure for estimating the logistics of the study, a sample of 300 eligible new-borns per centre was used. This will fulfil the requirement that the sample size at birth should be at least four times larger than the group of 70 children to be followed up longitudinally for two years.

In the cross-sectional study, as for the longitudinal study, 70 children per age range are required. As mentioned, to improve the estimates of growth in the fifth year, it will be necessary to expand the upper age limit of the cross-sectional study to 71 full months. The lower age limit was set at 18 months to provide some overlap with the longitudinal study. Since three-month groupings are used, then 1260 children aged 18 to 71 full months are needed in each centre, allowing for refusals, a sample of 1400 per centre was used. The sampling methodology for the cross-sectional study is adapted to each site depending on local circumstances (e.g., a household survey in the catchment areas of the maternity hospitals included in the study).

8. POSSIBLE SOURCES OF BIAS

Building a prescriptive reference may be affected by methodological problems. ' section reviews two major sources of bias and how these will be addressed.

8.1 Dropouts and self-selection bias

The issue of selectivity was a major concern of the Expert Committee (W 1995a). Whenever only a small proportion of the population is eligible for ente the study, other important selection biases may operate. To counteract possibility, several steps are being taken: operational definitions of the fee recommendations are somewhat relaxed to ensure that a greater proportio children are included in the study; the study is restricted to sites where 20% or r of the mothers in the subpopulation of interest are likely to comply with t definitions; and breast feeding support is being provided to enhance compliance.

Possible differences between children selected for inclusion in the curve anc remaining children will be assessed by comparing the baseline measuremen birth (weight, length and head circumference) of children selected for the study all children born in the same facilities as well as all children in the socio-econc subpopulation of interest who refused to participate or were not eligible due to of intent to breastfeed. In addition, a sub-sample of the latter group of childr visited at 12 months, to compare their attained weights and lengths with thos the cohort children.

Finally, the growth of children who complied with the feeding recommend will be compared with that of children who entered the study but failed to con This entails continuing to follow up to the age of two years all children include the study, whether or not they comply.

8.2 Variability

The Expert Committee expressed concern that selecting children who were similar" (e.g., in feeding practices) might lead to low variability and therefo outer percentile lines that are too close to the median (WHO 1995a). This w result in over-diagnoses of both growth deficits and excess (e.g., obesity) whe curve is used in a general population. In order to minimise this problem, data be combined from different parts of the world, thus allowing the international set to include ethnic and environmental variability that is not present in 1 existing growth curves. In addition, there will be no anthropometric restriction eligibility: the subpopulations to be included will have a spread of mean l weights, and no anthropometric restrictions will be made on individual chil therefore ensuring substantial variability in anthropometric measurements at t Recent research showed that breast-fed infants growing in different parts of the w have remarkably similar growth patterns and low variability compared to the cu NCHS-WHO reference (WHO 2000). This finding confirmed the earlier results o Expert Committee (WHO 1995a) suggesting that concern with lack of variat may not be as important as originally believed.

9. CONCLUDING REMARKS

The WHO Multicentre Growth Reference Study is an ambitious undertaking. By prescribing the nature of the sample to the degree proposed by the protocol, the recommended approach represents a significant departure from approaches used in the past to construct growth references. This approach has been adopted because of the stated intent to create a reference that also approximates a standard. Thus the proposed reference should be representative of a group whose care reasonably approaches recommended health practices. At the time of this writing data collection, involving about 10,000 children, is well underway in six countries representing all the major world regions: Brazil, Ghana, India, Norway, Oman and the USA. It is envisaged that the new reference will be available in the year 2004.

10. REFERENCES

de Onis, M., and Habicht, J.P., 1996, Anthropometric reference data for international use: recommendations from a WHO Expert Committee. American Journal Clinical Nutrition, 64, 650-658.

Kramer, M.S., 1987, Determinants of low birthweight: methodological assessment and meta-analysis. Bulletin of the World Health Organisation, 65, 663-737.

Mansbach, I.K., Greenbaum, C.W., and Sulkes, J., 1991, Onset and duration of breast feeding among Israeli mothers: relationship with smoking and type of delivery. Social Science and Medicine, 33, 1391-1397.

Meyer, M.B., 1979, Breast-feeding and smoking. Lancet, 1, 975-976.

Vio, F., Salazar, G., and Infante, C., 1991, Smoking during pregnancy and lactation and its effect on breast milk volume. American Journal Clinical Nutrition, 54, 1011-1016.

WHO, 1995a, Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. Technical Reports Series No. 854. Geneva, WHO.

WHO, 1995b, Working Group on Infant Growth. An evaluation of infant growth: the use and interpretation of anthropometry in infants. Bulletin of the World Health Organisation, 73, 165-174.

WHO, 1997, Working Group on the Growth Reference Protocol. A growth curve for the 21st Century: the WHO Multicentre Growth Reference Study. Geneva: WHO Department of Nutrition.

WHO, 2000, Working Group on the Growth Reference Protocol and the WHO Task Force on Methods for the Natural Regulation of Fertility. Growth patterns of breast-fed infants in seven countries. Acta Paediatrica, 89, 215-222.