

## 7. DISCUSSION

The intrinsic biological complexity of the dynamics of human growth made the construction of the standards presented in this report more challenging than was the case for the attained growth standards (WHO Multicentre Growth Reference Study Group, 2006a; 2007). This section seeks to provide guidance for the use and interpretation of the standards based on insights gained during construction of the velocity standards and feedback from clinicians who participated in reviewing and field-testing the velocity tools.

The standards are presented for the age span birth to 24 months. They include weight, length and head circumference centiles conditional on age, in variable measurement intervals. Additionally for weight, empirical centiles of velocity in 1- or 2-week intervals from birth to 60 days are presented. With the exception of tables 15 and 17 (velocity in g/d), all velocity tools of the WHO Child Growth Standards are increment standards describing the distribution of growth increments over variable intervals. As is the case for attained growth, the standards presented in this report are sex-specific. Appendix B summarizes specifications of the BCPE models for each of the growth velocity standards.

### *Velocity conditional on age*

The overall pattern of the (age-conditioned) centiles depicts the age-dependent changes in velocity that characterize human postnatal growth. Growth progresses at a rapidly decelerating rate from birth, reaching a near-plateau by the end of the first year and continues to taper off gently through the second year. This is the expected overall pattern of growth under conditions of adequate nutrition and psychosocial care with no chronic infections or unusual rates and/or severity of acute infections: the pattern that underpins the general expectation that infants will double their weight by age 6 months and triple it by 12 months. However, examination of individual growth trajectories has shown saltatory increments in short ( $\leq 24$  hours) intervals followed by periods (2-63 days) of no measurable growth (Lampl et al., 1992). Although the intervals (1- to 6-months) presented for the main age-conditioned tools of these standards cannot capture the short-span saltation and stasis described by Lampl and co-workers, the growth velocities of individual children in the WHO standards are characterized by very high variability in consecutive growth intervals. It is not unusual for a child to grow at the 95<sup>th</sup> velocity centile one month and at the 20<sup>th</sup> the next while continuing to track on the attained weight-for-age chart. Alternating or irregular patterns of high and low velocities may occur in successive periods even in the absence of morbidity. With regard to weight, losses or slow gains (related to morbidity or otherwise) in a given period are normally followed by higher velocities, likely indicating catch-up growth.

The 1-, 2-, 3-, 4- and 6-month increment tables are independent of each other and the clinician should use the one that most closely approximates the interval over which the child is seen. For example, the centile corresponding to an increment between age 2 and 3 months is not associated with the centile corresponding to half of the increment in the 2-month interval between ages 1 and 3 months. This is because one cannot expect the growth rate in a given 2-month period, except perhaps at the median, to be the sum of the two corresponding 1-month intervals.

With specific reference to weight, negative increments occur generally after 6 months of age and are captured in the lowest centiles. They coincide with the weaning period, when children are more exposed to food contamination, and when they become more active and start to explore their environment. Others who have developed velocity references have observed similar losses (WHO Working Group on Infant Growth, 1994), even if final published figures did not include them since only a narrow range of centiles were presented (Guo et al., 1991; Roche et al., 1989). It is important to note that losses that are tolerable in short intervals might not be acceptable in longer intervals. For example, the 5<sup>th</sup> centile indicates a loss of about 100g between 10 and 11 months and also between 11 and 12 months (Table 4), which can be acceptable for 1-month intervals at that age. However, the

same 5<sup>th</sup> centile for a 2-month interval at the same age (10 to 12 months) indicates a gain of about 30g (Table 6), implying that there was time for recovery within the longer interval.

### *Alternative approaches to constructing conditional weight gain references*

Others have approached the construction of conditional weight gain references by applying methodologies that adjust not only for age but also for regression to the mean (Wright et al, 1994; Cole, 1995; Cole, 1997). The theoretical basis for this approach is the expectation that over time infant weights drift towards the median from the tails of the distribution. Using this approach, weight gain is calculated in terms of the change (compared with the initial measurement) in the infant's attained weight SD score adjusted for regression to the mean (Cole, 1995). The formula for this calculation hinges on the correlation between the initial and second SD scores, which determines the expected slope of the change in the child's size between the two points of measurement. Despite its theoretical advantages, calculation of this conditional gain SD score requires computerization and thus limits the potential for its application. In effect, this approach has not gained currency in clinical settings.

To explore how conditional gain SD scores compare with the increment centiles presented in this report, the published methodology (Cole, 1995) was applied for adjusting for regression to the mean on 1- and 2-month interval weight increments (results are presented in Appendix C). The first step was to calculate the attained weight-for-age (WA) z-score for each child at each of the visits. Next, the respective correlation matrices for the 1- and 2-month intervals were derived. Then, the published formula to calculate  $SD_{\text{gain}}$  (the z-score associated with the change in WA z-score between visits) was applied. The  $SD_{\text{gain}}$  values were compared with z-scores of the age-conditioned 1- and 2-month weight increments.

Plots of empirical densities showed that the distributions of the z-scores from the two methods overlap for each respective test interval (figures C1 and C2). Distributions of pairwise differences between the z-scores from the two methods were also examined (figures C3 and C4). Ninety percent of the differences were between -0.33 and +0.34 (for 1-month intervals) and between -0.27 and +0.29 (for 2-month intervals).

To assess the magnitude of the impact of regression to the mean, two sets of children were selected: one in the lower bound (WA z-scores between -2.5 and -1.5) and the other in the upper bound (WA z-scores between +1.5 to +2.5) of attained growth at the start (time1) of specified intervals. The change in their z-scores at the end (time2) of 1- or 2-month periods were examined to observe what proportion deviated from the assumption of regression to the mean (Table C1).

For the lower bound (time1 z-scores between -2.5 and -1.5), the results were consistent with regression to the mean only for initial ages 0-1 months and 0-2 months, i.e. WA drifted further from the median for 21% and 13% of children, respectively. For the remaining ages, 30-52% (1-month intervals) and 28-47% (2-month intervals) of weights shifted further from the mean, contrary to shifts that would have reflected regression to the mean. Similar findings were observed for the upper bound (time1 z-scores between +1.5 and +2.5) i.e. 27% (age 0-1 month) and 20% (age 0-2 months) drifted away from the mean. In the older age groups, this tendency was observed for 37-55% (1-month intervals) and 30-54% (2-month intervals). As expected, corresponding average changes in WA z-scores were, relatively high at ages 0-1 or 0-2 months (in the assumed direction of regression to the mean), but they dropped rapidly thereafter to near 0.

In summary, growth in snapshots of 1- or 2-month intervals was consistent with regression to the mean between birth and 1 or 2 months but the phenomenon was much less evident at later ages. Differences between individual z-scores when applying the two methods were relatively minor. This

raises questions regarding the impact those differences have on clinical management and the method's conceptual and practical accessibility for users in disparate settings. For the age period when the largest impact of regression to the mean is observed, as described below this report provides sex-specific centiles for weight increments conditional on birth weight in 1- and 2-week intervals from birth to 2 months.

### *Tables of weight velocity from birth to 60 days*

These tables present physiological weight losses that occur in the early postnatal period but that are not usually included in available reference data.

In-depth comparisons between the sexes were made in the process of deriving these centiles. In most cases, boys' net increments in the 2-week intervals between 14 and 60 days were higher than girls' increments by values of 50-100 g. The differences in the first two weeks (birth to 7 and 7-14 days) were less clear-cut, but it was interesting to observe that the weight losses (depicted in the 5<sup>th</sup> and 10<sup>th</sup> centiles) between birth and day 7 were slightly attenuated in girls compared to boys.

It was not possible to estimate from these data precisely when infants should recover their birth weight following weight loss that is common in the first few postnatal days. Net increments at the median (0 to 7 days) are positive for both boys and girls, suggesting that recovery of birth weight could be achieved in less than one week. Considering the 25<sup>th</sup> centile (0 g increment from birth to 7 days), the data suggest that 75% of newborns recover their birth weight by day 7. It is understood that recovery depends on what percentage of birth weight was lost and successful initiation of lactation. However, rather than focus only on weight gain, it is important to adopt a holistic approach by looking at the child's overall health status and clinical signs. This involves also assessing mother-child interaction, indicators of successful breastfeeding such as infant breastfeeding behaviour and the timing of stage II lactogenesis (i.e. the onset of a copious milk supply), and breastfeeding technique (position and attachment), as these are necessary for maintaining successful infant nutrition. The overall breastfeeding profile and some aspects of its initiation among the infants included in these standards were published elsewhere (WHO Multicentre Growth Reference Study Group, 2006d).

The complexity of growth velocity is not adequately reflected in the usual presentation of gross estimations of growth rate over wide age spans. Such estimations overlook the dramatic changes that characterize growth in the first few months and the high variability within an individual child's growth rate in succeeding intervals. These centiles (birth to 60 days) provide a description of weekly and biweekly changes in velocity, illustrating the inadequacy of rules of thumb such as "infants should gain 200 g/week or 30 g/d in the first 3 months".

Centiles are presented both for net increments and for velocity in g/d. It is important to note that the g/d figures are not the simple average of the gross gains or losses reported in corresponding weekly and fortnightly tables. The g/d figures are derived by calculating individual daily increments for newborns in each of the birth weight categories and then estimating centiles directly from the raw g/d values. When mother-child dyads experience breastfeeding difficulties in the early postpartum period, lactation performance and weight gain are monitored every few days, hence increments per day are likely to be handier to use than weekly or fortnightly increments. Even in the absence of such difficulties, visits to the clinic take place at random ages, and these daily increments offer a flexible option for evaluating growth over fractions of the tabulated time blocks. It is important to note that the g/d figures, particularly in the first week, are composite figures reflecting, on average, losses followed by recovery.

Contrary to speculation that weight velocity would vary by birth weight, the centiles from the various birth-weight categories were very similar, leading to the conclusion that velocities can be collapsed into a single column. Low or high anthropometric values observed in the WHO standards represent the physiological extremes of normality among children in the absence of intrauterine growth problems. If this were not the case, a negative correlation between birth weight and early growth rate would have been more likely because postnatal catch-up and catch-down growth would have been observed.

### *Minimum weight gain tables*

Tables of weight gain conditional on starting weight were requested by users of the table of "expected minimum gains in weight" in community-based growth promotion programmes mainly in Central America (Griffiths et al., 1996; Griffiths and McGuire, 2005). The AIN (*Atención Integral al Niño*) tables were developed using data from 112 children born between 1972 and 1974 and followed from birth to 2 years by the *Centro Latinoamericano de Perinatología* (Martell et al., 1981). The values of expected weight do not take into account sex or age, and it appears that the weight gain selected as the minimum was the 25<sup>th</sup> centile; otherwise, little is known about them (Martorell et al., 2002). The original AIN table provides single values of expected minimum weight gains in 30-day or 60-day intervals relative to the child's starting weight.

Tables of 1- and 2-month weight gains conditional on starting weight were produced and circulated for peer review. Reviewers rejected them on substantive grounds, and they were thus excluded from the final standards.

Firstly, the basic assumption of the AIN table, i.e. that young children of the same weight grow at the same rate irrespective of age, is flawed. In the WHO standards, starting at 5 kg, there is a significant negative association between age and final weight. This implies that younger children at the same starting weight end up with a higher final weight after 1- and 2-month intervals compared to those at older ages.

Secondly, it is impossible to select "expected minimum weight gains" that would be appropriate for all infants or children with the same starting weight. Such values are bound to be too low for some infants/children and too high for others of the same starting weight. Moreover, the selection of single minimum thresholds introduces the notion of centile tracking in velocity that is contrary to normal physiological growth in individual children. In the WHO standards, the probability of two consecutive 1-month or 2-month weight increments falling below the 5<sup>th</sup> centile is 0.3%. If the 15<sup>th</sup> centile is chosen, this probability increases to only 2% and 1.8%, respectively.

Thirdly, as infants grow older the lower centile values (25<sup>th</sup> and below) become less than the day-to-day variability in weight, making detection of a minimum weight at this level impossible. Examining the 1-month interval centiles for boys, for starting weights greater than about 8.5 kg, the 25<sup>th</sup> centile value for final weight is only 100 g greater than the starting weight. The day-to-day variability (SD) is about twice this level. For girls, 100 g differences are seen between starting and 25<sup>th</sup> centile final weights at even lower weights, e.g. about 8 kg. For girls that start at 12.7 kg, the 25<sup>th</sup> centile final weight is 100 g less than the starting weight. The situation is even worse if the 15<sup>th</sup> or 5<sup>th</sup> centiles are selected (e.g. examining the 1-month interval for girls, a starting weight of 12 kg implies a loss of 100 g and 200 g in the final weight for the 15<sup>th</sup> and 5<sup>th</sup> centile, respectively).

### *Overall considerations*

**Measurement error.** Measurements of growth are subject to error from multiple sources. Faulty measurements can lead to grossly erroneous judgements regarding a child's growth. The accuracy of growth assessment is improved greatly if measurements are replicated independently and the values

averaged. This procedure minimizes the impact of faulty single measurements. MGRS measurements were undertaken to assure the highest level of reliability; and the final values used in the creation of these standards were an average of two observations, thereby minimizing random measurement errors in observed growth. This level of reliability is not typical in routine clinical measurement in primary health care settings; however, it can be achieved in research contexts (WHO Multicentre Growth Reference Study Group, 2006b) and where resources permit, in clinical situations caring for children at high risk of growth problems. The training course on child growth assessment is a tool to assist health care providers in the effective application of the WHO growth standards. It teaches, *inter alia*, the knowledge and skills needed to measure children correctly (WHO, 2008).

**Measurement intervals in field application.** Ideally, velocity assessment should be done at scheduled visits that coincide with the ages and intervals (1, 2, 3, 4 or 6 months) for which the centiles are presented. In practice, however, the timing of clinic visits is dictated by uncontrollable factors, and ingenuity will be called for in applying the standards. In constructing the standards, some variation was allowed around the intervals. For measurements made at ages 0-6 months, 6-12 months and 12-24 months, the allowable deviations from the exact planned age were  $\pm 3$  days,  $\pm 5$  days and  $\pm 7$  days, respectively. The practical advantage of this approach is that use of the standards allows for equally slight deviations without a need to correct observed increments through interpolation. For example, to assess a two-month increment between 11 months and 13 months of age the observed increment could be validly used as long as the first measurement was no more than 5 days early or late and the second measurement no more than 7 days early or late.

The simplest approach to dealing with measurement intervals beyond allowable ranges is to interpolate (i.e. prorate) observed increments to the relevant interval or to refer to the next larger interval if appropriate. For example, a boy weighed at 11 months returns at 13 months and 24 days having gained 600 g. If this increment is prorated to the 2-month interval 11-13 months, the estimated gain is 429 g ( $600 \text{ g}/84 \text{ days} \times 60 \text{ days}$ ), which is just below the 50<sup>th</sup> centile (458 g, Table 6). If the 3-month interval 11-14 months is referred to instead, there is no need to interpolate as the visit falls within the allowable difference ( $\pm 7$  days); his increment (600 g) also is just below the 50<sup>th</sup> centile (665 g, Table 8). The assumption made is that the rate of growth was constant over this period, but there is no alternative way of partitioning the increment.

If the observed interval is on target, say exactly 2 months, but the starting and ending ages do not coincide with those tabulated in the standards (e.g. an increment measured over the exact 2-month interval between 11.4 and 13.4 months of age), the recommended practical solution is to use the tabulated reference values for the 11 to 13-month age interval. Similarly, for an increment observed between 11.6 and 13.6 months of age one would use the reference values tabulated for the 12 to 14-month interval. It should be understood that these are compromises whose limitations are especially apparent in the first year when growth decelerates rapidly and the difference in velocity between consecutive periods can be large. For example, growth between 2.5 to 3.5 months carries equal contributions from 2-3 and 3-4 month intervals: a baby girl who gained 310 g would be classified as below the 3<sup>rd</sup> centile at 2-3 months and as below the 15<sup>th</sup> centile at 3-4 months. The best clinical judgement in such circumstances requires making a holistic assessment of the child's health. A more precise option in the forgoing case (i.e. when interval length is on target) is to interpolate the L, M and S values from consecutive age intervals and to calculate the child's z-score as described in Chapter 6.

**Clinical usefulness of growth velocity.** The questions that a clinician seeks to answer when using a velocity standard include whether a child's growth rate over a specified interval, or over a series of intervals, raises concern about underlying morbidity; or in the context of interventions to promote growth (e.g. in endocrinology), whether a given treatment produced the expected change in growth rate; or, for the newborn, if breastfeeding has been successfully established.

There are some fundamental differences between velocity and attained (distance) growth that affect how the increment standards should be used and interpreted. Chief among them is the lack of correlation between successive increments in healthy, normally growing children. For individual attained growth curves, the variability in successive z-scores tends to be minimal over short periods (there are high correlations between successive attained values). This "tracking" is not usually seen for successive individual growth velocities. For example, as indicated earlier, the probability of two consecutive 1-month or 2-month weight increments falling below the 5<sup>th</sup> centile is 0.3%. If the 15<sup>th</sup> centile is chosen, this probability increases to only 2% and 1.8%, respectively. Normally growing children can have a very high z-score one month and a very low one the following month, or vice versa, without any underlying reason for concern. Thus, a single low value is uninformative; only when velocities are repeatedly low should they cause concern. Nevertheless, very low z-score values, even if observed only once, should raise the question of whether there is underlying morbidity within the holistic clinical assessment of the child.

Some authors recommend that two successive increments below a cut-off like the 5<sup>th</sup> centile be used (Roche and Sun, 2003). Others suggest that consecutive increments below the 25<sup>th</sup> centile should signal growth problems (Healy et al., 1988). Healy and co-workers chose this limit on the basis that the chance of a false positive diagnosis (i.e. a normally growing child with two successive increments below this centile) is approximately 6.25% ( $0.25^2$ ). This raises an important question: Does the interval matter, for example, if these low velocities occur in two consecutive 1-month versus 3-month intervals? We think it does when we consider the cumulative effect of growth deficits. Future research will need to determine what patterns of successive velocity thresholds over which specified intervals have the best diagnostic and prognostic validity for specific diseases. The need for this type of clinical research applies to both high and low velocities.

During periods of severe illness (e.g. prolonged diarrhoea), one would expect very low velocity followed by compensatory high velocity (catch-up). During catch-up growth, one would expect successive increments to be repeatedly in the higher ranges. An important difference with attained growth is that single extreme values of increments are comparatively less worrisome. For example, z-scores above +6 and below -6 for attained growth are observed only in very rare conditions like severe dwarfism, gigantism, severe cachexia and extreme obesity. However, such extreme z-score values may be seen during the assessment of growth velocity. Ultimately, growth velocity must always be interpreted in conjunction with attained growth, as the position on the attained growth chart is essential to interpreting the growth rate, e.g., low weight velocity if the child is overweight and catching down, or higher weight velocity reflecting catch-up growth when recovering from illness.