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Mid-upper arm circumference at age of routine infant vaccination to identify infants at elevated risk of death: a retrospective cohort study in the Gambia

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Objective To determine the predictive value for death before 12 months of age of mid-upper arm circumference (MUAC) and weight-for-length Z score (WFLz).

Methods A retrospective cohort analysis of infants living in Keneba, in rural Gambia, was conducted. Anthropometric measures were obtained from demographic surveillance system records for infants registered between February 1974 and July 2008 who had had MUAC and WFLz recorded at 6–14 weeks of age and vital status recorded at least once more. Hazard ratios (HRs), population attributable fractions and areas under receiver operating characteristic (ROC) curves were estimated to assess the predictive value for death in infancy of MUAC and WFLz.

Findings Of 2876 infants included in the analysis, 40 died before the age of 12 months. The HR for death in this group versus in well-nourished infants was 5.8 (95% confidence interval, CI: 1.6–21) for a WFLz < −3. HRs for MUACs below the thresholds of 115 mm, 110 mm and 105 mm were 4.5 (95% CI: 1.4–15), 9.5 (95% CI: 2.6–35) and 23 (95% CI: 4.2–122), respectively. The attributable fractions for a MUAC < 130 mm and a WFLz < 0 were 51% and 13%, respectively. The areas under the ROC curve for death in infancy were 0.55 (95% CI: 0.46 to 0.64) for WFLz and 0.64 (95% CI: 0.55 to 0.73) for MUAC.

Conclusion Among infants aged 6 to 14 weeks, unadjusted MUAC showed good performance in identifying infants at increased risk of death.

Introduction

Recent estimates indicate that 8.5 million infants less than 6 months of age throughout the world are wasted by World Health Organization (WHO) growth standards, which define wasting as a weight-for-length Z score (WFLz) of < −2.3 The risk of undernutrition in infancy is increased in preterm and low-birth-weight infants and in infants born to young, rural, poorly nourished mothers of lower socioeconomic or educational status.4–6 Additionally, in poor regions, low rates of exclusive breastfeeding and mixed feeding as early as 2 months of age expose infants to contamination and to foods with low nutrient density.7

Anthropometric measures and suitable thresholds for intervention are normally assigned on the basis of their predictive value with respect to death, ideally calculated using data from untreated populations. However, a lack of data for infants aged under 6 months,8 among whom mortality is higher than in any other paediatric age group, makes it difficult to interpret anthropometric measures to guide interventions in this age group.

Among children aged 6 to 60 months, simple anthropometric indices are strongly associated with the risk of death.9–14 For children aged 0 to 60 months, WHO recommends using WFLz to define wasting;9 since WFLz is a measure of undernutrition adjusted for height and therefore independent of stunting in its description of wasting. For any given anthropometric measure, a Z score indicates how many standard deviations below or above a reference median an individual value is found. According to WHO growth standards, WFLz below the cut-off value of −3 standard deviations (SDs) from the median defines severe wasting (also called severe acute malnutrition); WFLz below the cut-off value of −2 but no lower than −3 defines moderate wasting (also called moderate acute malnutrition).15 In children aged 6 to 60 months, the mid-upper arm circumference (MUAC), with simple cut-offs, is at least as predictive of death as WFLz.16–20 Within this age group, adjusting MUAC by calculating the Z score or adjusting for height does not improve MUAC’s predictive value.21 MUAC can be measured easily, quickly and affordably. Values below the cut-offs of 125 mm and 115 mm are used to define moderate and severe acute malnutrition, respectively. MUAC is currently not recommended for use among infants aged below 6 months because of a lack of data on its reliability, measurement in practice and predictive value for death. However, we recently reported that in rural Kenya the inter-observer reliability of MUAC among infants aged 0 to 6 months was greater than that of WFLz.22

In the last two decades, infant vaccination coverage in rural Africa has greatly improved.23 Attendance at well baby clinics provides an opportunity for vaccination, nutrition and health screening and intervention. Our primary aim was to use data from a long-standing demographic surveillance system (DSS) in the Gambia to determine whether MUAC, measured at the age when infants attend clinics for routine vaccination (i.e. between 6 to 14 weeks), can predict all-cause infant death. Additionally, we aimed to compare the association between MUAC and infant death with that between WFLz and infant death, as well as to discuss potential MUAC cut-off values for use in infants 6 to 14 weeks of age.
**Methods**

**Study site**

Since 1974, the British Medical Research Council has maintained a field station in Keneba, the Gambia. The site comprises the villages of Keneba, Manduar and Katong Kunda and is collectively known as “Keneba”. Keneba has been under a longitudinal Demographic and Health Survey system since 1949. The population is predominantly composed of Muslim subsistence farmers with similar socioeconomic status, cultural beliefs and practices. Due to their proximity to each other, the three villages experience a similar climate, with a short rainy season between June and September (wet hungry season) and a longer, dry “harvest” season between October and May.

**Age, anthropometric measurements and death**

Before 1975, village births and deaths were reported weekly to the DSS team in Keneba through Arabic-literate village informants, included in the DSS team to ensure the accuracy of the information obtained from the allocated households. However, since 1975 birth dates have been obtained from postnatal care clinic and hospital records, in addition to village informants.

The anthropometric data described in this study were collected by trained health workers (nurses and midwives) during monthly well baby clinics (established in Keneba in 1975), during postnatal care clinic visits (at 6 weeks and 3 months of age), or through the periodic DSS survey. Hospital deaths were ascertained using hospital records and home deaths using village informants.

All data on deaths in hospital and at home deaths using village informants.

**Study design**

We conducted a retrospective cohort analysis of longitudinal data from infants 6 to 14 weeks old who were followed until 12 months of age. The primary outcome was death within 12 months of the date of birth.

**Statistical analysis**

Data were analysed using STATA 12. Absolute measures of MUAC and length were excluded from the analysis if they were not biologically plausible for infants aged 6 to 14 weeks (i.e. MUAC < 70 mm; length < 400 mm or > 750 mm). WFLz categories were then defined according to the WHO growth standards.

The number of deaths “plateaus” at a MUAC of approximately 130 mm and a WFLz of 0. We therefore chose as the reference category a MUAC greater than or equal to the cut-off value of 130 mm (which also approximates the median MUAC for three-month-old infants in the WHO growth reference population), and we investigated MUAC thresholds of 115 mm, 110 mm and 105 mm. For WFLz, we chose WFLz ≥ 0 as the reference category and investigated integer thresholds of −1, −2 and −3.

We used the Kruskal–Wallis test to detect median differences in MUAC and WFLz and the χ² test for trend to detect associations between the proportion of infants who died and different anthropometric categories. We used Cox proportional hazards regression to compare hazards of mortality between anthropometric categories. Hazard ratios (HRs) for dying by 12 months of age were estimated for MUAC and WFLz in two ways. First, HRs were estimated by comparing individual MUAC and WFLz measures with the reference categories (i.e. ≥ 0 for WFLz and ≥ 130 mm for MUAC). Then, to examine the performance of potential cut-off values, we estimated HRs by defining exposure as MUAC or WFLz below each of the thresholds that we
investigated. The HRs were adjusted for exact age in days at visit, sex, decade and season of birth and are presented with their 95% confidence intervals (CIs). According to one study, children born during June to October in the Gambia are at elevated risk of death, although more recent evidence suggests that this effect is waning. We also controlled for decade of birth because, since the data span four decades, we wanted to account for changes in the health system or other temporal effects. We estimated the sensitivities and specificities of MUAC and WFLz and used receiver operating characteristic (ROC) curves to assess their discriminatory ability to predict death by 12 months of age. To

assess the contribution of MUAC and WFLz to infant mortality, we calculated the sample attributable risk following the method of Garenne et al., which considers nutritional status and relative hazards as continuous variables.

**Ethical considerations**

Ethical approval was granted by the Gambian government/Medical Research Council Laboratories Joint Ethics Committee (L2008.82vs01, 11 November 2008) and the London School of Hygiene and Tropical Medicine Ethics committee (21 July 2009).

**Results**

**Baseline characteristics**

A total of 3541 infants aged between 0 to 12 months were registered in the Keneba DSS between February 1974 and July 2008. Of these infants, 56 died before they reached 12 months of age. MUAC measurements taken at the age of interest (6–14 weeks) were missing for 556 (16%) infants, 125 of whom had their initial records generated before the age of 6 weeks and 431 after the age of 14 weeks. Ninety six (3%) infants were non-residents of Keneba; 13 (0.4%) infants could not be traced after recruitment (Fig. 1). A total of 2876 infants were included in the analysis (equivalent to 839 747 child–days of observation); their median age at enrolment was 61 days (interquartile range, IQR: 53–76 days). Of these infants, 2033 (71%) were recruited during the long dry season.

At recruitment, the median WFLz was 0.15 (IQR: −0.65 to 0.93) and the median MUAC was 121 mm (IQR: 114–130). Wasting (WFLz < −2) was present in 144 (5%) infants (Table 1). MUAC and WFLz both showed distributions that varied significantly by season of birth (P < 0.01) but not by decade of birth.

Forty infants died and 147 infants were censored between recruitment and 12 months of age (Fig. 1). The median values for age, MUAC, weight and length did not differ significantly between the censored and uncensored infants (P > 0.05). Of the 125 infants whose first record was generated before 6 weeks of age, 5 died before reaching the age of 12 months (Fig. 1). The proportion of infants who died increased as MUAC and WFLz decreased (χ² test for trend P < 0.001) (Table 1).
Predictive value

WFLz identified very few of the 40 infants who subsequently died. Only 3 of these 40 infants had a baseline WFLz < -2. WFLz was only significantly associated with death at values < -3, whereas MUAC categories of < 115 mm, < 110 mm and < 105 mm were associated with HR estimates of 4.5 (95% CI: 1.4–15), 9.5 (95% CI: 2.6–35) and 23 (95% CI: 4.2–122), respectively (Table 1).

Severe wasting (WFLz < -3) predicted death before 12 months of age with a sensitivity of 7.5% (95% CI: 2.5–20) and a specificity of 98% (95% CI: 97–99), whereas MUAC < 105 mm predicted death with a sensitivity of 20% (95% CI: 11–35) and specificity of 93% (95% CI: 92–94) (Fig. 3). The area under the ROC curve for predicting death was 0.55 (95% CI: 0.46–0.64) for WFLz and 0.64 (95% CI: 0.55–0.73) for MUAC (Fig. 3). Although the point estimate for MUAC was higher, this difference was not statistically significant at the conventional level (P = 0.07).

The cumulative attributable risk associated with values of WFLz < 0 within the study population was 13.0%, while that associated with a MUAC ≤ 130 mm was 51.7% (Fig. 4).

Discussion

We have shown that a single MUAC measurement in infants around the age of vaccination (6–14 weeks) has predictive value with respect to infant death. Contrarily, WFLz had poor predictive value with respect to infant death: the CIs of the area under the ROC curve included 0.5, which suggests that the WFLz values observed were not significantly different from those that would be obtained by randomly allocating children to different risk of death categories. The observed HR for MUAC < 110 mm was broadly comparable to reported pooled odds ratios for all-cause deaths associated with severe wasting among children aged less than 5 years.53 WFLz identified very few of the infants who died and thus had low sensitivity for predicting infant death.

Little has been published on the use and interpretation of anthropometric measurements in infants aged less than 6 months. A recent study using data from Ghana, India and Peru reported that moderate wasting (WFLz < -2 but ≥ -3) observed during the first immunization visit (i.e. between weeks 6 and 10 after birth) poorly predicted death before 6 months of age.39 Our findings are concordant with those of this study, which also show that, in the age group of infants aged 6 to 14 weeks, a WFLz < -3 identified a very small proportion of the infants at risk of dying. Similar findings have been reported among infants aged 0 to 12 months in the Congo.60 Although the age range in this study was broader than ours, the finding suggests that the WFLz cut-offs in current use may be of little value in discriminating younger infants at higher risk of death. Several factors may explain the poor discriminatory and predictive value of WFLz. First, it is possible that WFLz is inaccurately or unreliable measured in infants aged less than 6 months.22,62 Second, WFLz is a very indirect measure of muscle and fat mass, unlike MUAC. These body compartments, and in particular muscle mass, seem important for health and survival.15,43

Currently, MUAC is not being measured in infants aged less than 6 months because of lack of evidence to direct its interpretation. In children aged 6 to 60 months, MUAC shows a known bias towards identifying younger and smaller infants as malnourished14 and the rapid growth experienced by younger infants may make it difficult to establish an appropriate single MUAC cut-off value. In this study we minimized the effects of this age-selection bias by adjusting the hazard model for the infant’s exact age in days and by cutting off the MUAC measurement in infants aged less than 5 months.
limiting the analysis to an age band of 6 to 14 weeks, which coincides with the age range for routine infant vaccination. The idea was to use a selection criterion that would enhance the operability of our findings within the existing health system. In the case of infants who do not access routine vaccination services, MUAC could also be measured routinely as part of active community-based screening. However, because of improved vaccination coverage throughout Africa, the proportion of infants likely to be missed using this criterion is expected to be small. 13 Further studies exploring the use of MUAC to assess the nutritional status of infants aged less than 6 months are recommended to gather evidence from which to determine the optimum age bands for its use.

A potential MUAC threshold

In our analysis, we focused on investigating the sensitivity, specificity and positive predictive value of MUAC and had intended to use the findings as criteria for selecting an appropriate threshold for this measure, as suggested by Myatt et al. 17 We found that most deaths in the study population were associated with MUACs below a threshold of 130 mm. Specifically, 36% of the deaths in infancy would hypothetically be prevented if MUAC among infants aged 6 to 14 weeks were sustained above a cut-off of 110 mm, whereas practically no deaths would be prevented if WFLz were sustained above −3.

It makes sense to use a MUAC value that identifies infants at high risk of death but likely to benefit from intervention. Thus, the best MUAC cut-off depends on the potential effectiveness and cost-effectiveness of any intervention that might be applied. 17 In the absence of these data, information on predictive and discriminatory value are used instead to define cut-offs. Although in our study infants aged 6 to 14 weeks with MUAC <115 mm had a fourfold greater risk of dying than those with MUAC ≥130 mm, this 115 mm cut-off identified about one fourth (27%) of the infants in the sample and hence lacks specificity (Table 1). This finding does highlight, however, the need to improve nutrition in the general population.

From our data, a MUAC cut-off of less than 105 mm would be highly specific in that it would select 7% of the total infant sample, specifically the fraction with a dramatically elevated risk of death (HR = 23). These infants are probably too sick to survive even when treated or require a highly intensive and invasive therapeutic intervention to be rehabilitated. On the other hand, a MUAC cut-off of 110 mm is less specific and would select 14% of the target population, i.e. the fraction having a risk of death nearly 10 times higher than well-nourished infants (HR = 9.5). This 110 mm cut-off may identify a group of infants who, if not acutely ill, could probably benefit from home-based preventive, low-intensity interventions focused on breastfeeding, micronutrient supplementation, good hygiene and prevention of infections. Thus, the choice of a MUAC cut-off value depends on the type of interventions available. The selected cut-off should be tested in practice and verified across various settings.

Study strengths and limitations

To examine the relationship between MUAC in early infancy and death in the first year of life we relied on data from a well-maintained and well-resourced surveillance system with good anthropometric data covering four decades. This data source lends strength to our findings. However, one important limitation of our study is that only 40 deaths were observed among the 2876 infants who were followed up to 12 months of age. This very low death rate, which has been previously noted in Keneba, is believed to result from direct and indirect exposure to improved health interventions in this DSS setting, where research has been conducted for many years. 22 Thus, the presence of the DSS might have undermined our ability to detect the association between anthropometric measures and survival. It may be impossible to find another prospective cohort for validating MUAC cut-offs, but historical data from older cohorts is feasible and can also serve the purpose. Another important limitation is that the direct causes of death of the infants could not be ascertained because they had not been systematically registered in the DSS. While accurate cause-of-death data would be of considerable interest, collecting it is not easy. Verbal autopsy methods have very poor sensitivity for the most common causes of death in the age group we studied, including pneumonia and gastroenteritis. 33,46 Importantly, the studies that have sought to establish anthropometric criteria for malnutrition in children aged 6 to 60 months have relied on estimates of all-cause mortality rather than cause-specific mortality. 13,14

Conclusion

In infants aged 6 to 14 weeks, which is the age of routine vaccination, MUAC below 115 mm identifies infants more likely to die before the age of one year than well-nourished infants. MUAC can be accurately, affordably and reliably measured with ease, and we recommend measuring it during routine infant vaccination. In the absence of data on the effectiveness of interventions for the management of malnourished infants in a given context, we suggest using a MUAC cut-off of 110 mm to identify infants with a markedly increased risk of death. Research on appropriate clinical guidelines for the treatment of severe acute malnutrition in infants aged less than 6 months is needed to support effective interventions.

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Objectif Détecter la valeur prédictrice de décès avant l’âge de 12 mois sur la base de la conférence du bras à mi-hauteur (ou périmètre brachial, soit PB) et du score centré réduit poids-pour-taille (WFLz).

Méthodes Une analyse de cohorte rétrospective a été effectuée sur des nourrissons vivant à Keneba, dans la Gambie rurale. Les mesures anthropométriques ont été extraits des dossiers du système de surveillance démographique pour les nourrissons inscrits entre février 1974 et juillet 2008, dont le PB et le WFLz avaient été enregistrés entre 6 et 14 semaines, et dont le statut vital avait été enregistré au moins une fois par la suite. Les ratios de risque (RR), les fractions étiologiques du risque et les zones sous les courbes de caractéristique de fonctionnement du récepteur (ROC) ont été estimés pour évaluer la valeur du périmètre brachial et du WFLz afin de prédire le décès des nourrissons.

Résultats Sur 2 876 nourrissons inclus dans l’analyse, 40 sont morts avant l’âge de 12 mois. Le RR de décès dans ce groupe, par rapport aux nourrissons bien nourris était de 5,8 (95% IC: 1,6-21). MUAC en valeur centile 115 mm, 110 mm et 105 mm et WFLz < -3 est de 5,8 (95% CI: 1,4-15) et WFLz < -2 est de 9,5 (95% CI: 2,6-35) et WFLz < -1 est de 23 (95% CI: 4,2-122). MUAC < 130 mm et WFLz < 0 de 4,2 à 122. Le RR de décès dans le groupe des nourrissons bien nourris était de 5,8 (95% CI: 1,4-15) et WFLz < -3 est de 9,5 (95% CI: 2,6-35) et WFLz < -2 est de 23 (95% CI: 4,2-122). MUAC < 130 mm et WFLz < 0 de 4,2 à 122. Le RR de décès dans le groupe des nourrissons bien nourris était de 5,8 (95% CI: 1,4-15) et WFLz < -3 est de 9,5 (95% CI: 2,6-35) et WFLz < -2 est de 23 (95% CI: 4,2-122). MUAC < 130 mm et WFLz < 0 de 4,2 à 122. Le RR de décès dans le groupe des nourrissons bien nourris était de 5,8 (95% CI: 1,4-15) et WFLz < -3 est de 9,5 (95% CI: 2,6-35) et WFLz < -2 est de 23 (95% CI: 4,2-122). MUAC < 130 mm et WFLz < 0 de 4,2 à 122. Le RR de décès dans le groupe des nourrissons bien nourris était de 5,8 (95% CI: 1,4-15) et WFLz < -3 est de 9,5 (95% CI: 2,6-35) et WFLz < -2 est de 23 (95% CI: 4,2-122). MUAC < 130 mm et WFLz < 0 de 4,2 à 122. Le RR de décès dans le groupe des nourrissons bien nourris était de 5,8 (95% CI: 1,4-15) et WFLz < -3 est de 9,5 (95% CI: 2,6-35) et WFLz < -2 est de 23 (95% CI: 4,2-122). MUAC < 130 mm et WFLz < 0 de 4,2 à 122. Le RR de décès dans le groupe des nourrissons bien nourris était de 5,8 (95% CI: 1,4-15) et WFLz < -3 est de 9,5 (95% CI: 2,6-35) et WFLz < -2 est de 23 (95% CI: 4,2-122). MUAC < 130 mm et WFLz < 0 de 4,2 à 122. Le RR de décès dans le groupe des nourrissons bien nourris était de 5,8 (95% CI: 1,4-15) et WFLz < -3 est de 9,5 (95% CI: 2,6-35) et WFLz < -2 est de 23 (95% CI: 4,2-122). MUAC < 130 mm et WFLz < 0 de 4,2 à 122. Le RR de décès dans le groupe des nourrissons bien nourris était de 5,8 (95% CI: 1,4-15) et WFLz < -3 est de 9,5 (95% CI: 2,6-35) et WFLz < -2 est de 23 (95% CI: 4,2-122).
Резюме

Определение младенцев с повышенным риском смертности при измерении округлости середины плеча в возрасте плановой вакцинации: ретроспективное когортное исследование в Гамбии

Цель Определить прогностический уровень младенческой (в возрасте до 12 месяцев) смертности измерения округлости середины плеча (ОСП) и расчета индекса массы тела Z-score (ИМТ).

Методы Был проведен ретроспективный когортный анализ младенцев в Кенебе, сельской местности Гамбии. Антропометрические данные были получены на основе результатов системы демографического мониторинга новорожденных, зарегистрированных в период с февраля 1974 года по июль 2008 года, у которых проводилось измерение ОСП и расчет ИМТ в возрасте 6-14 недель и имелись результаты обследования состояния здоровья, проводившегося повторно. Для определения прогностического уровня младенческой смертности измерения ОСП и расчета ИМТ были проанализированы отношения рисков (ОР), площади и добавочные доли популяционного риска под графиком зависимости чувствительности от частоты ложно положительных заключений (ROC-кривая).

Результаты Из 2876 младенцев, включенных в анализ, 40 скончались в возрасте до 12 месяцев. ОР смертности в этой группе по сравнению с младенцами, имевшими полноценное питание, составил 5,8 (95% доверительный интервал, ДИ: 1,6-21) для ИМТ < -3. ОР для ОСП ниже порогового значения 115 мм, 110 мм и 105 мм составили 4,5 (95% ДИ: 1,4-15), 9,5 (95% ДИ: 2,6-35) и 23 (95% ДИ: 4,2-122) соответственно. Добавочные доли популяционного риска для ОСП < 130 мм и ИМТ < 0 составили 51% и 13% соответственно. Площади под ROC-кривой младенческой смертности составили 0,55 (95% ДИ: от 0,46 до 0,64) для ИМТ и 0,64 (95% ДИ: от 0,55 до 0,73) для ОСП.

Вывод Среди младенцев в возрасте от 6 до 14 недель нескорректированные показатели ОСП оказались действенными в определении младенцев с повышенным риском смертности.

References

Anthropometry and mortality in infants in rural Gambia
Martha K Mwangome et al.


