Weight-for-age z-score as a proxy marker for diarrhoea in epidemiological studies

Wolf-Peter Schmidt,¹ Sophie Boisson,¹ Bernd Genser,² Mauricio Barrete,² Kathy Baisley,¹ Suzanne Filteau,¹ Sandy Cairncross¹

ABSTRACT

Background The validity of unblinded randomised trials testing interventions against diarrhoea is severely compromised by the potential for bias. Objective proxy markers for diarrhoea not relying on self-report are needed to assess the effect of interventions that cannot be blinded. Short-term changes in weight-for-age z-score (WAZ) may (due to catch-up growth) not be a clinically important marker for nutritional status. However, even a transient decrease in WAZ could indicate recent diarrhoea, and be interpreted as the effect of an intervention.

Methods Using data from two large vitamin A trials from Ghana and Brazil, the immediate effect of the cumulative diarrhoea occurrence over 14 and 28 day time windows on WAZ was explored.

Results A very strong linear association was found between the number of days with diarrhoea over the last 14–28 days and WAZ. In both trials, differences in diarrhoea between the trial arms were associated with corresponding differences in WAZ.

Conclusion Repeated WAZ measures appear to be a suitable proxy marker for diarrhoea in children, but have disadvantages in terms of specificity and study power.

INTRODUCTION

Diarrhoeal diseases continue to be a major cause of mortality and morbidity in children. Control measures have had some success in recent years. Treatment of diarrhoea with oral rehydration is effective in reducing case fatality. Preventive measures have proved more difficult. It is hoped that in the future rotavirus vaccination may contribute to reducing diarrhoea-related mortality in poor settings. However, it is possible that diarrhoea will remain a leading cause of child mortality worldwide also in the future. Some of the most challenging global issues, such as nutrition, environmental pollution, population increase and climate change are not only closely related to each other, but also have the potential to contribute to living conditions associated with a high risk of diarrhoea. There is clearly an ongoing need for large-scale epidemiological studies to test new interventions against diarrhoea.

In the past, trials testing, for example, water, sanitation and hygiene interventions have demonstrated large reductions in diarrhoea incidence and prevalence, often ranging from 30% to 50% disease reduction (figure 1). However, the comparison of blinded and unblinded randomised trials testing the effect of household water treatment (one of the few environmental interventions against diarrhoea that can be blinded) suggests that observer and responder bias in the collection of self-reported diarrhoea data may be substantial. Even an observed reduction in reported diarrhoea of 50% may be compatible with no true effect (figure 1). A study on a portable filter device conducted in Ethiopia found a 25% reduction of reported diarrhoea despite very low and inconsistent use, a result that is best explained by bias. It must be assumed that results from trials testing other unblinded interventions against diarrhoea, such as hand washing or sanitation, include a similar degree of bias. Empirical studies in other research fields, for example, clinical epidemiology, also found strong evidence for substantial bias due to lack of blinding.

Public health policy decisions aiming at reducing the burden of diarrhoea are severely compromised by this lack of reliable data on the effect of interventions, which may lead to favouring the implementation of clinical interventions that can be tested in double-blind randomised trials. Biased effect estimates may also cause interventions against diarrhoea to be scaled up prematurely, perhaps drawing attention away from other, possibly more beneficial public health measures. Alternative measures of diarrhoea that do not depend on self-report are needed to improve confidence in studies measuring the effect of unblinded diarrhoea trials. Diarrhoea-specific or overall mortality is a good outcome measure from the public health perspective, but mortality studies require a large sample size, which is beyond the scope of most trials. Health care utilisation (preferably self-initiated, not referred to by a field worker) has been used as an outcome measure in the past, but bias in healthcare seeking behaviour cannot be fully excluded. Other potential proxy markers for diarrhoea include inflammatory markers, and antibody titres against specific organisms, but results so far have been inconclusive. Also, conducting laboratory tests in large studies is logistically challenging and cost-intensive.

Finally, the effect of an intervention on diarrhoea may be estimated from its effect on nutritional status. The effect of diarrhoea on weight and height is well documented in the literature. The long-term effect of diarrhoea on height and weight may be particularly pronounced in children under 6 months, and appears to be modified by many factors such as breast feeding. Weight may be an inadequate marker for nutritional status, because the effect of diarrhoea on weight is thought to be rather short term and perhaps of little clinical importance. However, if weight, measured, for example, as weight-for-age z-scores (WAZ), is used only as a proxy marker for diarrhoea...
such concerns are irrelevant. It does not matter whether the observed weight loss is clinically important or largely due to transient effects of diarrhoea such as dehydration, loss of appetite, or an empty digestive system, and quickly reversed by catch-up weight gain. Although most studies on the effect of diarrhoea on nutritional status have tried to estimate the longer term effect of diarrhoea on weight, this analysis focuses on the immediate effect of diarrhoea on weight. The aim is to explore whether WAZ (which can be measured quite easily by field workers with basic training) can be used as a proxy marker of diarrhoea.

**METHODS**

**Study populations**

Data from two large trials testing the effect of vitamin A supplementation on diarrhoea and other illnesses were used. The trials were conducted in northern Ghana and north-eastern Brazil both in semi-arid low-income settings, between 1990 and 1991. The Ghana study took place in a poor rural setting with extended families living in compounds and practicing subsistence farming. The study area was chosen due to a high prevalence of vitamin A deficiency. All compounds in the study area were included in the trial. All children aged 0-60 months living in these compounds were eligible for inclusion. The study was a dynamic cohort including newborn children and excluding children growing older than 60 months. The Brazil trial was conducted in Serrinha, a town with 30,000 inhabitants 170 km north-west of Salvador, the capital of Bahia state. At the beginning of the study, children were identified by a census of the poorest neighbourhoods in the area. Eligible children were between 6 and 48 months of age, and had no active xerophthalmia, recent measles or recent vitamin A supplementation. In both trials children were followed up for approximately 1 year, with approximately 10% of person time lost to follow-up (table 1). Socioeconomic status was poorer in Ghana, where a large majority of households relied on open wells, bore holes and rivers as water sources. In Brazil, over 95% of households had piped-in water supply and over 90% had electricity.

**Diarrhoea measurement**

Both studies aimed at obtaining continuous daily records of diarrhoea, from which diarrhoea prevalence over the last 2 weeks could be obtained for the purposes of this analysis. In Ghana, weekly field worker visits measured the daily prevalence of diarrhoeal disease symptoms since the last visit; in Brazil field workers visited up to three times a week. In the Ghana dataset, diarrhoea was defined based on mothers’ definitions and local disease perception. In the Brazil data, diarrhoea was defined as the occurrence of three or more loose stools over 24 h.

It has been recognised that the adverse effects of diarrhoea such as malnutrition depend not so much on the number of diarrhoea episodes, but on the duration of these episodes as well as the number of days with diarrhoea over a certain period of time, also known as the longitudinal prevalence. Therefore, a measure of recent diarrhoea was the number of days with diarrhoea in an individual during a fixed time window looking back from the date on which weight was measured. In order to focus on the short-term effect of diarrhoea on WAZ, a 14-day window was used for the primary analysis. In a secondary

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**Figure 1** All an illusion? Combined estimates of the effect of environmental health interventions on diarrhoea. The first four estimates are from systematic reviews including random effects meta-analysis. The estimate of the effect of blinded household water treatment interventions is a simple average from the few published and unpublished studies, as no valid data on the SEs were available. The effect size is given for illustration only - none of the blinded studies showed any evidence for an effect of the intervention on diarrhoea.

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**Table 1** Epidemiological characteristics of the two study populations

<table>
<thead>
<tr>
<th></th>
<th>Ghana</th>
<th>Brazil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children</td>
<td>1877</td>
<td>1209</td>
</tr>
<tr>
<td>Person years</td>
<td>1455</td>
<td>1104</td>
</tr>
<tr>
<td>Age range at baseline (months)</td>
<td>0–59</td>
<td>6–48</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate/PY</td>
<td>9.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Longitudinal prevalence</td>
<td>17%</td>
<td>5%</td>
</tr>
<tr>
<td>Mean duration of episodes (days)</td>
<td>6.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Mean WAZ by age at measurement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–12 months</td>
<td>–1.56</td>
<td>–0.51</td>
</tr>
<tr>
<td>&gt;12–24 months</td>
<td>–1.86</td>
<td>–0.89</td>
</tr>
<tr>
<td>&gt;24–36 months</td>
<td>–1.70</td>
<td>–0.81</td>
</tr>
<tr>
<td>&gt;36–48 months</td>
<td>–1.57</td>
<td>–0.84</td>
</tr>
<tr>
<td>&gt;48–60 months</td>
<td>–1.63</td>
<td>–0.89</td>
</tr>
<tr>
<td>0–60 months</td>
<td>–1.67</td>
<td>–0.83</td>
</tr>
<tr>
<td>WAZ &lt; –2</td>
<td>30%</td>
<td>13%</td>
</tr>
<tr>
<td>Mean HAZ</td>
<td>–2.39</td>
<td>–1.30</td>
</tr>
<tr>
<td>HAZ &lt; –2</td>
<td>62%</td>
<td>25%</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths (n)</td>
<td>77</td>
<td>4</td>
</tr>
<tr>
<td>Mortality rate/1000 PY</td>
<td>52.9</td>
<td>3.6</td>
</tr>
</tbody>
</table>

PY, person years of observation; WAZ/HAZ, weight/height-for age z-score.
Figure 2  Association between diarrhoea in the last 14 days and weight-for-age z-score (WAZ) in two vitamin A trials in Ghana and Brazil. Diarrhoea was treated as a categorical variable with 0 (zero) days of diarrhoea in the last 14 days as reference.

The effect of the intervention (vitamin A) on WAZ was analysed using random effects linear regression adjusted for repeated measurements in a child. The analysis was adjusted for the baseline WAZ measurement prior to the intervention. The effect of the intervention on the number of diarrhoea days over the 14 days prior to anthropometric measurements was analysed using random effects Poisson regression. The analysis was done in STATA 10 (StataCorp, Texas, USA).

RESULTS

Epidemiological and growth status characteristics of the two study populations are shown in table 1. The children in Ghana had a higher risk of diarrhoea, underweight (WAZ<−2), growth faltering (HAZ<−2) and death. The mean duration of diarrhoea episodes was much longer in Ghana than in Brazil.

In a first step, the number of diarrhoea days in the past 14 days was treated as a continuous variable. All analyses were adjusted for age at the time of measurement (restricted cubic spline), which did not influence the slope but narrowed the confidence intervals. In Ghana, WAZ declined by 0.018 with every additional day with diarrhoea (95% CI −0.020 to −0.016), in Brazil by 0.022 (95% CI −0.028 to −0.015). In a post hoc analysis, a trend was found suggesting that the association between diarrhoea and WAZ was slightly stronger in children under 24 months compared to over 24 months (choosing 12 months of age as cut-off point showed similar results). In Ghana, the regression coefficients for children under or above 24 months were −0.019 and −0.013 respectively (test for interaction p=0.07). In Brazil, the regression coefficients were 0.029 and 0.021 respectively (test for interaction p=0.08).

Figure 2 shows the results of the regression analysis with the number of diarrhoea days in the past 14 days treated as a categorical variable, with no (zero) diarrhoea days as reference. In both study populations there is a very pronounced linear association between diarrhoea and WAZ. In a post hoc analysis, a trend was found suggesting that the association between diarrhoea and WAZ was slightly stronger in children under 24 months compared to over 24 months (choosing 12 months of age as cut-off point showed similar results). In Ghana, the regression coefficients for children under or above 24 months were −0.019 and −0.013 respectively (test for interaction p=0.07). In Brazil, the regression coefficients were 0.029 and 0.021 respectively (test for interaction p=0.08).

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In a post hoc analysis, a trend was found suggesting that the association between diarrhoea and WAZ was slightly stronger in children under 24 months compared to over 24 months (choosing 12 months of age as cut-off point showed similar results). In Ghana, the regression coefficients for children under or above 24 months were −0.019 and −0.013 respectively (test for interaction p=0.07). In Brazil, the regression coefficients were 0.029 and 0.021 respectively (test for interaction p=0.08).

Analysis, 28-day windows were also tested. Weight measurements preceded by fewer than 14 days (or 28 days) of observation were excluded from the analysis.

Weight measurement

Weight and height were measured monthly for 1 year in the Ghana study, and four times in the Brazil study (at baseline, and then every 4 months). The first measurement in the Brazil data was excluded as no diarrhoea data were available prior to the measurement.

In both trials, measurements of length/height and weight were taken in duplicate by two independent trained field workers who were blinded to the intervention. The final measurement was the mean of these two measurements. Weight was measured by using hanging scales in Ghana and by electronic scales in Brazil. Weight and height were transformed into z-scores (WAZ and HAZ), indicating how many standard deviations an individual child of a certain age deviates from the norm. The WHO growth norms were used for the Ghana data (using the WHO Anthro software http://www.who.int/childgrowth/software/en/) and the national growth standard for Brazil (calculated previously). HAZ was included in the analysis as a control for the analysis. It was expected that an effect of diarrhoea would be seen over the last 2 weeks on WAZ but not on HAZ.

Statistical analysis

Linear regression analysis was used with WAZ (or HAZ) as the outcome variable and the number of diarrhoea days over the 14 days preceding the day of weight or height measurement as the exposure variable. The analysis was adjusted for repeated measurements in a single child using fixed effects linear regression. Specifying a fixed effects model allowed exploring exclusively the within-child effect of diarrhoea on WAZ/HAZ, excluding potential confounding due to children with high risk of diarrhoea also having lower WAZ/HAZ scores unrelated to diarrhoea. In both Ghana and Brazil, older children had on average lower WAZ than children under the age of 12 months. At the same time, older children had less diarrhoea than younger children. Therefore, age needed to be included as a confounding variable. Age was included in the model by constructing a restricted cubic spline (three knots), as the association between age and diarrhoea was non-linear.
The association between recent diarrhoea and WAZ was also apparent when using a 28 day window instead of a 14 day window for recent diarrhoea. In Ghana, WAZ declined by 0.013 standard deviations with every additional day with diarrhoea (95% CI –0.014 to –0.012), in Brazil by 0.014 SDs (95% CI –0.018 to –0.010). Figure 4 shows the results of the regression analysis with the number of diarrhoea days in the past 28 days treated as a categorical variable, again with no (zero) diarrhoea days as reference, confirming the linear association between recent diarrhoea and WAZ.

Finally, it was tested whether the effect of the intervention (vitamin A) on diarrhoea and WAZ were correlated. In Ghana, vitamin A had no effect on diarrhoea prevalence. The overall prevalence ratio (PR) was 1.01 (95% CI 0.89 to 1.14). However, if follow-up time was restricted to the 14 days prior to an anthropometric measurement, there was slight decrease in diarrhoea in the intervention arm (PR = 0.97, table 2). The above analyses suggested that a reduction in diarrhoea should translate into an increase in WAZ. Accordingly, there was a slight increase in WAZ by 0.04 in the intervention arm (table 2).

In the Brazil study, vitamin A was overall associated with a 10% decline in diarrhoea longitudinal prevalence (proportion of time ill) (PR = 0.90, 95% CI 0.78 to 1.03). However, if the follow-up time is restricted to the 14 days prior to an anthropometric measurement, the treatment arm experienced slightly higher longitudinal prevalence (PR = 1.03, table 2). Again, there were corresponding changes in the WAZ with a slight decrease of 0.03.

(Note that the overall results for Ghana and Brazil slightly deviate from the published data, since a slightly different common analysis method was used for both datasets.)

**DISCUSSION**

The results demonstrate a strong linear relationship between diarrhoea in the last 2–4 weeks and weight for age z-score in children under the age of 5, suggesting that WAZ may be a suitable proxy marker to measure the effect of an unblinded intervention against diarrhoea. Many previous diarrhoea trials, especially those testing the effect of vitamin A intervention, have been conducted under conditions where diarrhoea is prevalent, and the effects on growth have not been assessed.

**Figure 3** Association between diarrhoea in the last 14 days and height-for-age z-score (HAZ) in two vitamin A trials in Ghana and Brazil. Diarrhoea was treated as categorical variable with 0 (zero) days of diarrhoea in the last 14 days as reference.

**Figure 4** Association between diarrhoea in the last 28 days and weight-for-age z-score (WAZ) in two vitamin A trials in Ghana and Brazil. Diarrhoea was treated as categorical variable with 0 (zero) days of diarrhoea in the last 28 days as reference.
interventions on diarrhea, have either not included WAZ as an outcome measure at all, or have measured weight only at the beginning and end of the intervention period (eg, 10 23). According to this analysis, observing a strong reduction in self-reported diarrhea, as is often the case in unblinded diarrhea trials (figure 1), but failing to find larger mean WAZ compared to the control arm may speak against a true effect of an intervention on diarrhea.

The major drawback of WAZs may be their low specificity. Many conditions, for example, fever or respiratory infections, can acutely alter appetite, hydration, metabolism and weight. Using WAZ as a proxy for diarrhea is, therefore, most appropriate in trials testing an intervention that specifi-

Table 2  Effect of the intervention (vitamin A) on diarrhea in the 14 days before measurement of weight, and WAZ adjusted for baseline WAZ

<table>
<thead>
<tr>
<th>Study</th>
<th>Diarrhoea LP</th>
<th>Diarrhoea PR (95% CI)</th>
<th>WAZ difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghana</td>
<td>17.7%</td>
<td>−1.71</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>17.3%</td>
<td>0.97 (0.86 to 1.10)</td>
<td>+0.04 (−0.01 to 0.09)</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>0.97 (0.86 to 1.10)</td>
<td>+0.04 (−0.01 to 0.09)</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>4.9%</td>
<td>−0.82</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>5.1%</td>
<td>1.03 (0.82 to 1.29)</td>
<td>−0.03 (−0.06 to 0.00)</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>1.03 (0.82 to 1.29)</td>
<td>−0.03 (−0.06 to 0.00)</td>
<td></td>
</tr>
</tbody>
</table>

LP, longitudinal prevalence (i.e., proportion of time ill); PR, (longitudinal) prevalence ratio.

If the reduction in reported diarrhea should be unbiased, as is often the case in unblinded diarrhea trials, but have disadvantages in terms of specificity and study power. Wherever possible, blinding an intervention and using reported diarrhea or mortality is still the method of choice.7 Given that results of unblinded trials on reported diarrhea may have little or even no validity, demonstrating the presence or absence of changes in WAZ could allow improvement of the evidence base of diarrhea trials, especially those testing complex environmental interventions.

In conclusion, repeated measures of weight-for-age z-score appear to be a suitable and relatively objective proxy marker for diarrhea in unblinded trials, but have disadvantages in terms of specificity and study power. Wherever possible, blinding an intervention and using reported diarrhea or mortality is still the method of choice.7 Given that results of unblinded trials on reported diarrhea may have little or even no validity, demonstrating the presence or absence of changes in WAZ could allow improvement of the evidence base of diarrhea trials, especially those testing complex environmental interventions.

What this study adds

- In this analysis of two large randomised trials it was found that repeated measures of weight-for-age z-score could be used as a proxy marker for recent diarrhea experience, even if it may have little clinical importance as a measure for nutritional status.
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