Association between clinical type of diarrhoea and growth of children under 5 years in rural Bangladesh

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Background
The role of diarrhoea in the aetiology of growth retardation in young children remains controversial. To evaluate this, a population-based, longitudinal study of young children aged 6–48 months was conducted in Matlab, a rural area of Bangladesh, between May 1988 and April 1989.

Methods
Data obtained from 584 children were examined by one-year (n = 412) and 3-month (n = 1220) growth periods. Each growth period was analysed based on clinical types of diarrhoea, namely, non-diarrhoea, non-dysentery diarrhoea (diarrhoea without blood), and dysentery (diarrhoea with blood). Weight and height gains were compared among the study groups initially by one-way analysis of variance followed by multivariate analysis adjusting for potential confounding variables.

Results
Compared to non-diarrhoea and non-dysentery diarrhoea, dysentery was associated with significantly lower annual weight gain (1866 g [P < 0.01] and 1550 g [P < 0.05] versus 1350 g, respectively) and height gain (6.51 cm and 5.87 cm versus 5.27 cm [P < 0.01], respectively). Both 3-month dysentery and non-dysentery intervals were significantly associated with less weight gain compared to non-diarrhoea intervals (490 g and 522 g versus 637 g [P < 0.05], respectively). Dysentery intervals were also associated with significantly poorer height gain compared to other intervals (2.19 cm versus 2.42 cm [P < 0.05] and 2.46 cm [P < 0.01], respectively).

Conclusions
The growth of young children is strongly influenced by the clinical type of diarrhoea and the impact is dependent on the proportion of dysentery episodes in the total diarrhoeal burden.

Keywords
Bangladesh, children, diarrhoea, clinical type, dysentery, weight gain, height gain

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Diarrhoeal illnesses are well recognised as a major cause of morbidity and mortality in young children in many developing countries. However, their role in causing childhood malnutrition is controversial. Community-based prospective studies in developing countries have consistently demonstrated a significant negative association between diarrhoea and short-term (1–4 months) weight gain but the conclusions on short-term height gain are less consistent. The negative effects of diarrhoea on linear growth velocity over longer intervals (>6 months) were documented in some studies, while little or no such effects have been reported from several other studies.

One possible explanation for the discrepant observations is the heterogeneity of diarrhoeal illnesses. Most studies that examined the association between diarrhoea and growth considered diarrhoea as a single disease entity, and were not designed to identify potential differences due to different types of diarrhoeal illnesses. Studies that have looked at the effects of diarrhoea on growth by type of illness have suggested that certain aetiological (Shigella spp.) and clinical types (dysentery) are associated with significant growth retardation. While these studies were constrained by not accounting for the effects of other important confounding variables, such as socioeconomic factors, the findings, nevertheless, suggest variations in nutritional outcome by type of diarrhoea. Confirmation of this heterogeneity is of
public health significance in understanding the impact of diarrhoea on the growth of children, and subsequently, for the design of appropriate interventions.

Findings that contribute to this controversy include: lack of consistent evidence of sustained negative effect by type of diarrhoea, failure to demonstrate a significant improvement in nutritional status following reduction in diarrhoeal incidence, and less relative impact of diarrhoea on growth compared to other illnesses or low dietary energy intake. Consequently, a careful reappraisal of the association with proper recognition of the heterogeneous nature of diarrhoea is necessary to better define the nutritional impact and public health significance of diarrhoea in the community.

The main objective of this study was to examine the effects of diarrhoea by clinical type on both short- and long-term growth of children under 5 years in rural Bangladesh, while controlling for the effects of some important potential confounding variables.

Subjects and Methods

This study was conducted in three villages at the Matlab Field Station of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) where the Centre has maintained a diarrhoea treatment hospital and research activities since 1963. Details of the study villages and selection criteria have been reported elsewhere. Briefly, children aged 6–48 months, and permanently residing in the three selected villages were eligible for enrolment in the study. Informed written consent was obtained from the mother of each participating child before enrolment. In total, 584 children were enrolled in the study.

At baseline, sociodemographic information including parental education, land ownership, family income, water sources, latrine types, and other household characteristics was collected by trained health workers. Trained female community health workers (CHW), with a minimum eighth-grade education and permanently resident in the study villages, collected morbidity data by visiting each child every fourth day at home. The mother or the regular caretaker of the study child was asked a standard series of questions about her child’s daily stool frequency, and the consistency and presence or absence of blood in the stool on the day of the visit and in the preceding three days. An episode of diarrhoea was defined as ≥3 loose, liquid or watery stools, or any number of stools with blood in 24 hours. Three diarrhoea-free days were required to separate the consecutive episodes. Diarrhoea was further classified as dysentery if the stool contained blood in any day during the episode.

Anthropometric measurements were taken by trained research assistants at the time of enrolment and then monthly, following standard procedures. Each child was weighed nude or with light clothes to the nearest 0.1 kg with a Salter-type spring scale. The scale was calibrated daily against known weight before use. Recumbent length of all children under 36 months and the standing heights of children aged 36 months were measured to the nearest 0.1 cm using a locally constructed length board or height stick. Two trained and experienced workers took each measurement independently, and the mean of the two measurements was recorded as the actual value. As a part of the quality assurance the weight and height of 10% of the study children were measured on the following day. There was no significant difference between the first and the repeat measurement.

Data analysis

Different observation periods were chosen to examine the short- and long-term effects of diarrhoea on growth. Observations with complete diarrhoea surveillance data and anthropometric measurements both at the beginning and at the end of the respective observation periods were included in the analysis.

The short-term effects of diarrhoea on growth were examined in 3-month child intervals. Each child’s 3 calendar-month observation period constituted one child interval. Although multiple observations (child intervals) were available from one individual child, each child interval was assumed to be an independent observation. The number of observations (n) in the analysis refers to child intervals (3-month), and not children. However, the effects of diarrhoea on long-term growth were examined over a one-year period, and the number of observations (n) in that case referred to the number of children included in the analysis.

Each observation (3/12 months period) was classified by clinical type namely: non-diarrhoea (no diarrhoea during the period), non-dysentery (diarrhoea without blood) or dysentery (diarrhoea with blood) type of diarrhoea. Per cent time with diarrhoea was calculated for each observation, using the number of days with diarrhoea divided by the actual number of days observed during the respective analytical periods. This percentage was adjusted for 90 days in the case of child intervals and 365 days in the case of a one-year observation period.

Nutritional status was assessed at the beginning of each observation period by comparing the weight and height of the study children with the medians of the NCHS reference population of the same age and sex. Weight and height gains during the respective analysis periods were the main outcome variables and were determined by the difference between the last and the first measurements during the respective analysis periods and these figures were also adjusted for 90 days in the case of child intervals and for 365 days for a one-year observation period.

Spearman rank correlation was used for assessing the linear relationship between the independent and dependent variables. Mean weight and height gains were compared initially by one-way analysis of variance, and Duncan’s Multiple Range (DMR) test was used for examining any statistically significant difference in unadjusted means. All analyses were followed by a multivariate analysis controlling for age, sex, parental education, household income, land ownership, baseline nutritional status and per cent time with diarrhoea using the General Linear Model (GLM) in SAS version 6.04. In the multivariate models, independent variables with high correlation (Spearman correlation coefficient ≥0.7) were not fitted simultaneously. However, the variable more closely related to the hypothesis was always retained in the models. Variables that were significant at ≤0.1 level on univariate analysis were included in the multivariate model. The variables that were not significant at ≤0.1 level but were considered a priori to be confounders were also examined by fitting them into the multivariate model. Two-way interaction between diarrhoea variables and other independent variables was assessed for any effects on the outcome variables. Non-significant interaction terms were excluded from the final model.
Results

Of the 584 children enrolled, 512 were followed for one year, and the remaining 72 were followed for part of the year. Complete data were available for 1220 3-month child intervals and 412 one-year observations. Of the 1220 3-month child intervals, 184 children contributed four intervals each (184 × 4), 352 children contributed three intervals each (352 × 3), 412 two each (412 × 2) and another 512 children contributed one interval each (512 × 1). The main baseline characteristics of the 412 study children who had complete one-year data are presented in Table 1. The children were two and a half years old at enrolment and were of poor nutritional status as indicated by their mean anthropometric indices and the very high prevalence of underweight, stunting, and wasting. The overall mean incidence of diarrhoea was 4.5 episodes per child per year (median, 4 episodes/child/year; range, 0–13 episodes/child/year). Dysentery accounted for 15% of all diarrhoeal episodes. About 44% of the study children had at least one episode of dysentery, and one-half had at least one episode of non-dysenteric type of diarrhoea over the year. Only 5% of the children did not experience any diarrhoea during the study period. On average, children spent about 10% of the time with diarrhoea. However, over a quarter of the children had diarrhoea for more than 10% of the time, and another quarter had diarrhoea between 5% and 10% of the time during the year.

The mean annual weight and height gains were 1558 g and 5.8 cm. Both rate of weight and height gain decreased significantly with age ($\beta = -15$ g/month, $P < 0.001$; and $\beta = -0.11$ cm/month, $P < 0.01$, respectively). There was a significant positive correlation between height and weight gain ($r = 0.5$, $P < 0.001$).

None of the socioeconomic variables, all of which were considered as possible confounding variables, was found to have a significant association with annual or quarterly weight or height gain on univariate analysis. However, land ownership approached statistical significance. Children from households that owned land had a higher mean annual weight gain compared to those from the landless families (1578 g versus 1398 g, $P < 0.08$).

Clinical type of diarrhoea and short-term weight gain

Mean weight gain during the child intervals varied significantly by clinical type of diarrhoea (Table 2). Significantly greater weight gain was observed during non-diarrhoeal intervals compared to both non-dysentery and dysentery intervals. Although weight gain was less during the dysentery intervals compared to non-dysentery intervals, the difference was not statistically significant (Table 2). When the analysis was adjusted for age, sex, baseline nutritional status, parental education, household income, land ownership and per cent time with diarrhoea, the association among the adjusted means remained nearly the same (Table 2).

Clinical type of diarrhoea and annual weight and height gain

The results of one-way ANOVA showed that the mean annual weight gain varied significantly by clinical type of diarrhoea (Table 3). In the unadjusted analysis, although the unadjusted mean annual weight gain was the lowest among children with dysentery and the highest among non-diarrhoeal children, differences did not reach statistical significance on Duncan’s Multiple Range (DMR) test. On the other hand, the adjusted mean weight gain by the non-diarrhoeal children was significantly greater than that of non-dysentery or dysentery children. Between diarrhoeal children, the annual weight gain in the dysentery group was significantly lower than in the non-dysentery group (Table 3). The model explained 13% of variations in annual weight gain.

The adjusted annual height gain varied significantly by clinical type of diarrhoea (Table 3). Comparison of the adjusted means revealed that children who suffered dysentery had a significantly reduced annual height gain compared to non-diarrhoeal and non-dysenteric groups (Table 3).
Interactions were examined between diarrhoea and other independent variables for their effect on the outcome variables in all analyses. However, none of the interaction terms between clinical type of diarrhoea, and age, sex, nutritional status or socioeconomic factors reached statistical significance.

Discussion

Results of this study provide strong evidence that the effects of diarrhoea on growth in both the short- and long-term are associated with the clinical type of illness. Dysentery had the most deleterious consequences on both ponderal and linear growth although other types of diarrhoea showed a similar but relatively less strong negative association with growth. The loss of about half a kilo in annual weight gain, and one and a quarter centimetres in annual height gain was associated with dysentery in children under 5 in this population.

Regarding the limitations of this study, there was no control for other co-morbidities such as acute respiratory tract infections (ARI), malaria, etc., however, they were assumed to be equally distributed among the study groups. Energy and other nutrient intake were also not controlled. Lack of adequate power for certain comparisons rendered some important differences statistically non-significant. Furthermore, there were some unavoidable misclassifications in categorizing children or intervals by clinical type of diarrhoea as one single episode of dysentery during the observation period characterized the observation as dysentery. The negative effects of dysentery perhaps would have been amplified if this misclassification could have been avoided. In contrast, data collected using frequent surveillance (every fourth day) minimized the possibility of recall bias. Seasonal variations in diarrhoeal incidence and growth did not bias our findings since data for an entire year were analysed. The observed negative effect of dysentery on both short- and long-term growth has strong biological plausibility. Dysenteric episodes last relatively longer, and are associated with greater endogenous protein loss (protein losing enteropathy) than other types of diarrhoea. This endogenous protein loss might have greater biological significance, and be more detrimental to growth in children in developing countries where protein intake is generally low. Further, the high catabolic response to infection may also result in inadequacy among children with an apparently adequate intake.

Our results support the findings of an earlier study which observed no significant difference in the overall incidence of diarrhoea between two groups of children with different rates of growth but a higher overall incidence of dysentery among the children with poorer growth rates. The aetiology-based study also suggested that diarrhoeal illnesses caused by Shigella spp. had a longer-lasting negative effect on growth while those caused by enterotoxigenic Escherichia coli, commonly associated with watery diarrhoea, had no significant effect on long-term growth. This indicates that agents causing invasive diarrhoea and which normally manifest as dysentery have a substantial nutritional cost. Dysentery has been found to have a longer-lasting negative effect (evident up to 6 months after the episode) on the growth of young children in a community-based study.

The results of our study suggest careful interpretation of the findings of certain studies that showed reduction in diarrhoeal incidence had no effect on growth of children. Apart from...
lack of adequate power to show a significant difference in some of the comparisons, these studies did not mention which type of diarrhoea was most amenable to their intervention. Another recent study reported no significant effect of diarrhoea on child growth in a poor community where the comparison was based on growth trends in sufferers who had frequent (>9 episodes in 18 months) or infrequent (<4 episodes in 18 months) episodes of diarrhoea. However, the results of that study did not control for type of diarrhoea or duration of illness, both of which have great potential to confound the outcomes.

The controversy surrounding the relative importance of diarrhoea and inadequate dietary energy intake as causes of child malnutrition in developing countries also needs careful reappraisal. Those who believe that inadequate energy intake is the major cause of poor growth based their conclusion on indirect evidence. However, in one study the relative effects of diarrhoea and dietary energy intake on monthly weight gain were quantified. In that study, diarrhoea was used as a single disease entity although the same authors’ earlier study indicated that diarrhoeal effects on growth vary by aetiological type. It may be noted that the inadequacy of intake is assessed relative to recommended daily allowance (RDA), which is not necessarily the minimum requirement for optimal growth. Rather, RDA is a general recommendation for intake based on intake data from healthy populations. A recent study, based on a precise estimate of energy expenditure, suggested that the RDA for energy might be an overestimate of the actual requirement. More recent studies suggested a positive association between protein intake and growth, despite normal or low caloric intake. However, it may be possible that higher energy intake is associated with higher intake of proteins, vitamins and minerals. Conversely, very low energy consumption may be associated with compromised intake of other nutrients. Therefore, seemingly inadequate energy intakes frequently observed in developing countries might not be responsible for growth faltering although both low energy intake and malnutrition may co-exist.

The findings of this study clearly suggest that the proportion of dysenteric episodes in the total diarrhoeal burden is probably the most important determinant of the impact of diarrhoea on growth of young children. Although low energy intake is common among children who suffer from diarrhoea in developing countries, the literature on evidence to suggest that only improved dietary energy intake will result in better growth is limited. Therefore, to achieve the nutritional goal of diarrhoea control programmes, in addition to other general measures, more specific interventions aimed at reducing the incidence of dysentery, and the development of vaccines against common organisms causing dysentery should be emphasized.

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