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An Instrument for the Assessment of Diarrheal Severity in Community-Based Studies

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Title: An Instrument for the Assessment of Diarrheal Severity in Community-Based Studies

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Abstract:

Objective Diarrhea is a significant contributer to morbidity and is among the leading causes of death of children living in poverty. As such, the incidence, duration, and severity of diarrheal episodes in the household are often key variables of interest in a variety of community-based studies. However, there currently exists no means of defining diarrheal severity that are: (a) specifically designed and adapted for community-based studies; (b) associated with poorer child outcomes; and (c) agreed upon by the majority of researchers. Clinical severity scores do exist and are used in health care settings, but these tend to focus on relatively severe dehydrating and dysenteric disease, require trained observation of the child, and, given the variability of access and utilization of health care, fail to sufficiently describe the spectrum of disease in the community setting.

Design Longitudinal cohort study

Setting Santa Clara de Nanay, a rural community in the Northern Peruvian Amazon

Participants 442 infants and children 0-72 months of age

Main Outcome Measures Change in weight over one month intervals and change in length/height over 9-month intervals

Results Diarrheal episodes with symptoms of fever, anorexia, vomiting, greater numbers of liquid stools per day, and greater number of total stools per day, were associated with poorer weight gain compared to episodes without these symptoms. An instrument to measure severity was constructed based upon the duration of these symptoms over the course of a diarrheal episode.

Conclusions In order to address limitations of existing diarrheal severity scores in the context of community-based studies, we propose an instrument comprised of diarrhea-associated symptoms easily measured by community health workers and based on the association of these symptoms with poorer child growth. This instrument can be used to test the impact of interventions on diarrheal disease severity.

Strengths and Limitations of the Study:

-Intensive (three-times weekly) surveillence was used to capture symptoms of diarrheal severity in a community-based context, and to relate these to weight gain.

-Symptoms associated with severe disease, including dehydration and rectal temperature, limit the comparability of this instrument to existing diarrheal severity scores.

Introduction

Diarrhea is common cause of morbidity and mortality among children in the developing world (1). In addition to causing an estimated 0.75 million deaths per year (2), is estimated that the average child under five in the developing world will experience 2.9 episodes per year (3). The severity of these episodes is a common factor of interest in community-based epidemiological studies designed to test the impact of an intervention and/or quantify the burden of diarrheal disease (4).

Within the context of community-based studies diarrhea is defined as three or more loose stools per 24-hour period (5), prolonged diarrhea is diarrhea lasting between 7-13 days, and 'persistent' diarrhea as an episode of at least 14 days (6,7). These definitions were standardized in the early 1990s, leading to greater comparability between studies, and progress in the field.

Definitions of diarrheal severity, however, have remained variable (4). Clinical indicators of severity such as dehydration and dysentery (8) are associated with an acute risk of patient mortality and are used to guide therapy. These symptoms, in addition to need for hospitalization can define moderate to severe diarrhea among cases presenting for care at a healthcare center, but will not gradate between the majority of mild to moderate cases in the community (see **Figure 1**). As diarrhea case fatality rates decline, there is increasing interest in understanding the impact of mild-to-moderate disease on child health and development. For these episodes, there is a need for non-clinical measurement instruments adapted for use at a community level.

Several severity measurement instruments have been developed for classifying rotavirus diarrhea (9–11). However, these scores were not designed to differentiate severity of non-rotavirus diarrhea, which is less frequently associated with symptoms such as vomiting. Although rotavirus is the most frequently isolated pathogen among hospitalized diarrhea cases, there are other pathogens that are isolated more frequently in a typical community context. Furthermore, instruments that include hospitalization as a model input are problematic in settings where access to inpatient care facilities is heterogeneous, as can be observed in many low and middle-income settings.

Previous instruments included components such as rectal temperature and indexes of dehydration require either an invasive measurement or one that may be challenging to consistently measure across studies. These scales cannot be implemented in the context of community-based studies, where caregivers may not seek care for episodes of mild-to-moderate diarrhea and where surveillance is frequently bi-weekly or even weekly (12) and many episodes resolve in the interval between a study worker's regularly scheduled visits. While some studies have attempted to correct this problem through the creation of "modified" Vesikari scores (13,14), these scores were based on data from Canadian infants and HIV+ infants, respectively, making their findings less generalizable to the typical cases of pediatric diarrhea in the developing world.

Finally, the determination of severity in the formation of these instruments has generally been based on the empiric distribution of characteristics such as fever or dysentery associated with that particular cohort, rather than through association with morbidity (4).There are currently no instruments that

correlate on the high end to severe outcomes such as mortality and hospitalization, and on the middle-to-low end with other, more frequently occurring adverse health outcomes.

Acute weight loss associated with a diarrheal episode puts a child at risk of becoming underweight and/or wasted, outcomes associated with an increased risk of mortality (15,16), further infectious disease (17) and future stunting (18). Poorer linear growth in early childhood is associated with long-term negative outcomes including poorer cognitive development (19), adult work capacity and income (20), and, for girls, poorer maternal heath (15). Therefore, short-term weight gain and medium-to-long term linear growth are appropriate functional outcomes through which to validate measures of disease severity, and symptoms associated with poorer growth should be prioritized in the formation of diarrheal severity scores.

Using data from a previously-established longitudinal cohort with a high incidence of diarrhea and stunting and with standard community-based active surveillance measures, we evaluated the impact of diarrheal-associated symptoms on short-term weight gain in the subsequent temporal period. From this, we formed a diarrheal severity score to predict acute weight loss as well as depressed linear growth over longer temporal windows. This instrument may be validated for use in community based studies, clinical trials, and water, sanitation, and hygiene interventions.

Methods

Data were from a prospective, community-based study of 442 children 0-72 months of age living in the community of Santa Clara, located 15 km southeast of Iquitos, Peru. The cohort and study design were described previously (21,22); the overall objective was to explore the association between common etiologies of diarrhea and early childhood growth. The work described here was a prespecified secondary objective of the study.

From October 2002 – April 2006, participating families were visited three-times weekly by a trained health promoter to document the number and consistency of stools passed by the child over the previous 24-hour period, as well as other symptoms such as fever, anorexia, malaise, nausea, vomiting, stomach pain, and the reported presence of blood and mucus in the child's feces. This generated a continuous history of diarrheal disease over the surveillance period for each participating child (see **Figure 2**). Anthropometry was collected monthly, and socioeconomic and demographic information were collected during two community censuses before and during the study period. Diarrhea was defined by three or more semi-liquid stools reported over a 24-hour period, with episodes separated by at least three symptom-free days. Stool samples were collected as soon as possible after the case definition for diarrhea was met, and not more than two days after the episode ended. Fecal blood and fecal mucus, as reported by a lab technician, were also reported once per episode.

Symptoms associated with diarrhea were defined as having occurred during the diarrheal episode, if they were present on any day of the episode. The duration of symptoms associated with diarrhea was

defined as the number of days of the episode upon which the symptom occurred. Symptoms which were present the day before or the day after an episode of diarrhea were not counted.

Since persistent diarrhea is regarded as a separate epidemiological phenomenon with effects on growth apart from those of shorter episodes(23), only episodes of <14 days were retained in the analysis. In this cohort less than two percent of episodes were persistent (>=14 days = 1.5% of all episodes).

Statistical Methods

The percentages of episodes associated with a given symptom by age were tabulated and compared (ANOVA), and correlations and partial correlations between the presence of symptoms during an episode, and the duration of symptoms during an episode were calculated. All analysis was performed using Stata 11 & 12 (Statacorp, College Station, TX, USA).

Effects of Specific Symptoms on short-term Weight Gain

The effect of the presence of a symptom (see list of symptoms in **Table 1**) on a child's weight gain was modeled using change in weight of the child before versus after the episode. Only intervals in which a diarrheal episode was present were include in the model (i.e. episodes of diarrhea were compared to each other, and were not compared with periods in which no diarrhea occurred). Only episodes that occurred between two instances of anthropometry one month apart were considered, i.e., episodes which overlapped an anthropometric measurement were discounted. In order to avoid instances in which acute dehydration might have impacted weight gain, episodes that ended less than two days before anthropometry were also excluded. When more than one episode occurred within the same one month interval, only the episode of longer duration was retained in the model, and the total number of episodes in the month was considered as a covariate in the analysis. Sensitivity analysis was performed to determine the effect of these omissions on model outputs.

$$Wt_{ij} - Wt_{i-1,j} = b_j + \beta_0 + \beta_1 D_{symptom} + \beta_2 \sin_{season} + \beta_3 \cos_{season} + \ldots$$
$$+ \beta_4 Age\_Term\_1 + \beta_5 Age\_Term\_2 + \varepsilon_{ij}$$

(Equation 1).

The final model used to evaluate associations of symptoms with weight gain is shown in equation 1. $D_{symptom}$ represents the presence or absence of a symptom during the episode or the duration, in days, of the symptom during an episode (Column 2 of **Table 3**). Seasonal variation in weight gain was modeled by adding the terms $sine(\frac{2d\pi}{t})$ and $cosine(\frac{2d\pi}{t})$, where d is the day of the year, and t is 365 (24). Age Term 1 and Age Term 2 are fractional polynomials used to estimate the impact of age on monthly weight gain.

Formation of a Severity Score

Symptoms negatively associated with weight gain were categorized by duration and combined to form a severity score. When several symptoms were strongly correlated (rho>0.40), only the symptom that improved model fit was included in the severity score.

This score was then collapsed into three categories representing relatively mild, moderate, and severe diarrhea. The same model was then fit using the categorized variable. The unadjusted mean change in weight and weight for height Z score (WHZ) by severity category, and the adjusted one-month change in WHZ by severity category, were also estimated.

Effects of Specific Symptoms and Overall Severity on Linear Growth

In order to examine the relationship between individual symptoms and change in length/height, the cumulative incidence of episodes with and without each symptom was summed over nine-month intervals, and the effect of these episodes on linear growth (change in length/height) was modeled using the equation in Equation 2, where $D_{symptom\_present}$ is the cumulative incidence of diarrheal episodes in which the symptom occurred, and $D_{symptom\_absent}$ is the cumulative incidence of diarrheal episodes in which the symptom was absent, during the nine-month interval. The same seasonal terms and a set of fractional polynomial terms generated separately from those in the weight model were included. The models were also fitted with a child-level random intercept and a covariance structure that fixed a first-order autoregressive residual structure.

$$Ht_{ij} - Ht_{i-9,j} = b_j + \beta_0 + \beta_1 D_{symptom\_present} + \beta_2 D_{symptom\_absent} + \beta_3 \sin_{season} + \beta_4 \cos_{season} + \beta_5 AgeTerm\ \ 1 + \beta_6 AgeTerm\ \ 2 + \varepsilon_{ij}$$

(Equation 2).

The impact of episodes of varying severity, as categorized by the severity score developed above, was then tested similarly, using a model with three incidence terms, D_{mild}, $D_{\mathrm{mod}erate}$, and D_{severe}, representing the cumulative incidence of mild, moderate, and severe episodes in the nine-month interval, respectively. A similar model using nine-month change in HAZ as an outcome was used to test the effects of disease severity on HAZ.

Results

A total of 3,738 acute episodes were available for analysis. Of these, 2,461 were used in building the severity score (on the basis of being associated with anthropometry according to the criteria above, and with duplicate episodes in the same month discounted). Sensitivity analysis did not reveal any bias introduced by removing these episodes. Overall, 93.2% of the non-persistent episodes were associated with a lab result, of which 96.6% were collected within two days of the onset of the episode.

The symptoms considered in the analysis are reported in **Table 1**. The number of episodes associated with each symptom is shown in **Figure 3**. Most symptoms (all except anorexia and dysentery), were most common among the youngest children (<=2 years) and decreased in prevalence with age.

Correlations between the reporting of these symptoms during an episode ranged 0.018 to 0.643. The strongest correlations were between maternal report of blood and lab-reported blood (rho=0.643), followed by nausea and vomiting (rho=0.642), total depositions and liquid depositions >=4 (rho=0.589), maternal report of blood and maternal report of mucus (rho=0.586), malaise and stomach pain (rho=0.550), and malaise and anorexia (rho=0.427). All other correlations were less than 0.4. The correlations between the symptoms as categorized in the final severity score are reported below (**Table 2**).

Effects of Specific Symptoms on short-term Weight Gain

Anorexia, fever, malaise, vomiting and the maximum number of stools per 24/hour period, were all associated with poorer weight gain in months associated with diarrhea (p<=0.010). These symptoms were associated with 9.6 and 21.3 grams less weight gain per each day in the episode during which they occurred (**Table 1**).

The number of days in an episode with>=2, >=4, >=6, and >=8 liquid and or/semi-liquid stools were strongly correlated with each other. Of these, the number of days with >=4 liquid stools led to the greatest improvement in model fit and was therefore retained for further analysis. Each day in which >=4 liquid stools were present was associated with 23.3 grams less weight gain **(Table 1**).

Formation of a Severity Score

In total, six factors were found to be predictive of poorer weight gain: anorexia, malaise, vomiting, fever, the maximum number of stools per 24-hour period, and the number of days with 4 or more liquid per 24-hour period. Anorexia and malaise were strongly correlated (rho=0.432), and therefore only anorexia, which had the greater improvement in weight-model fit, was retained in the final severity score. Other symptoms were more weakly correlated when categorized by duration (rho <0.40) (**Table 2**). These variables were categorized into 4 levels according to the duration of the symptom (Table 3).The severity score was built by summing these five categorical variables **(Table 3** and **Figures 2** and **4)**.

Using this categorization process, episodes of moderate severity were found to predict 51.8g less weight gain over one month than episodes of mild severity (reference value), and episodes of high severity were found to predict 135.2 g less weight gain (**Table 4**). When change in WHZ was used as outcome, moderate and severe episodes predicted a loss of 0.049 and 0.182Z-scores over the month of the episode, respectively (**Table 4**).

Effects of Specific Symptoms and Overall Severity on Linear Growth

Of all the symptoms tested, only dysentery, as defined by laboratory-observed blood in stool, was independently predictive of poorer linear growth (results not shown). Because dysentery was not included in the severity score, it was then added as an independent variable to the model testing the impact of the severity score overall.

Incident episodes of low severity were not associated with poorer linear growth or changes in HAZ, while each episode of moderate severity predicted 0.041cm less linear growth and 0.010 less in HAZ.

Episodes of the highest severity were also unassociated with changes in linear growth and HAZ over the 9 month period (**Table 5**).

Discussion

During diarrheal episodes, anorexia/malaise, fever, vomiting, the number of days with >=4 liquid stools, and the maximum number of depositions per 24/hour period, were the symptoms most strongly associated with poorer weight gain. This suggests the prioritization of these symptoms in the formation of a severity score to characterize mild-to-moderate diarrhea in community-based study settings.

Several symptoms of potential interest were not collected and therefore could not be included in our analysis. Temperature, and the maximum number of instances of vomiting in a 24-hour period were not collected, which limits our ability to compare our severity score to that of the 20-point Ruuska and Vesikari score(11), and or the 24-point instrument proposed by Clark (9). Additionally, rectal temperature and dehydration were not noted, so a comparison of the index proposed by Ericsson and subsequently adapted by Jacobs et al could not be applied (25–27).These symptoms require the observation of the child by a trained health worker daily, i.e. a visit to the child at the moment of illness in addition to a caregiver's report. Our final severity score, which is based exclusively on information extracted from the verbal report of a caregiver during twice weekly visits, may have greater utility in a variety of community-based study designs where daily clinical assessments are not realistic. However, an ability to compare our severity score to those based on episodes observed in a clinical setting would be of methodological value(28).

Another weakness of our study was a relatively large number of "mild" episodes with a severity score of 0 or 1, and the relatively small number of "severe" episodes with a severity score >8 or above. Many episodes were of one or two days in duration, associated with a low (3 or 4) number of maximum stools per 24 hour period, and unassociated with any other symptom, and were therefore, difficult to differentiate between. These observations are consistent with the best available estimates of the proportion of categorization in mild, moderate, and severe episodes in the community setting (7).

In contrast, in the "high severity" category, there was a trend towards episodes of higher scores being associated with greater weight loss, i.e. an episode of severity score 15 had a greater impact than one of severity 8 (result not shown). However, because the number of episodes of greater severity was small, they were grouped in a single category.

In this index, we assess duration of symptoms differently than previous scores. Instead of episode duration being included as a separate variable, it was evaluated for inclusion for each symptom. We believe this is important in evaluating enteric disease caused by a range of both invasive and non-invasive pathogens where the illness syndrome is diverse. In contrast, previous severity scores have been built around the ability of a symptom to discriminate between pathogens: for instance, rotavirus

diarrhea is typically associated with significant vomiting and frequent stools, but relatively less fever, and the Vesakari index gives purging frequency and duration a high weight accordingly[1].

Dysentery, as defined by caregiver-reported or laboratory-technician reported visible blood, was not found to be a predictor of immediate episode-associated weight loss. However, it was independently predictive of poorer linear growth, a finding in agreement with other reports (29). The prevention of dysenteric diarrhea, which is associated with progression to persistent diarrheal (23) and mortality (30) merits prioritization. The importance of dysentery as a cause of linear growth faltering but not acute weight loss suggests that multiple measurement tools for diarrheal severity may be useful. In addition to acute weight loss and linear growth, factors such the likelihood of further infectious disease, the risk of acute dehydration (8), and the risk of mortality, are important child health outcomes that should be considered in score-building (**Figure 1**). The association between severity and the risk of hospitalization should also be considered (31), although measures such as hospitalization, which are dependent upon access and availability and not purely clinical need, vary according to local context and will need to be assessed in a variety of settings (32).

Standardized and carefully considered measures of diarrheal severity are desirable in clinical trials, intervention studies and descriptive community-based studies of diarrhea in the developing world (33), and would improve understanding of the impact of disease control measures on morbidity burden. The severity score we derived here is composed of simple components and allows for the meaningful classification of a diarrheal disease episode based upon the most common adverse events associated with diarrhea; depressed weight gain and poorer linear growth, an improvement over earlier scores built empirically around symptom frequency. The collection of the input data for this score is highly feasible and are likely available in many extant datasets; further validation could improve the estimates of diarrhea severity and disease burden across epidemiologic settings.

Contributors

MK conceived and designed the study. MK, MPO, PPY designed the data collection tools, monitored recruitment and data collection for the study, and supervised the study. PPY managed and cleaned the data. GL designed and implemented the analysis, CFW, LEC, REB, and DAS provided guidance during the analysis, and contributed to the interpretation of data. All authors helped write and critically review the article, and all authors have approved the final version to be published and agree to be accountable for all aspects of the work. MK and GL are the guarantors.

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[1] With a maximum of 6 points related to vomiting and a maximum of 3 related to fever.

Ethical Approval

This study was approved by the Institutional Review boards of the Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (IRB H.22.01.01.02.A), the US Naval Medical Research Center, Silver Springs, MD (IRB NMRCD.2002.0009), and Asociación Benéfica PRISMA, Lima, Peru (no IRB number). All participating families gave signed, informed consent before taking part in the study.

Competing Interests

We have read and understood the BMJ policy on declaration of interests and declare the following interests: None. All authors have completed the ICMJE uniform disclosure form at www.icjme.org/coi_disclosure.pdf (available on request from the corresponding author).

Declaration of Transparency

Gwenyth Lee confirms that this article is an honest, accurate and transparent account of the study reported, that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Data sharing

Raw data used in the analysis is available on request from the corresponding author at mkosek@jhsph.edu. Statistical code is also available upon request.

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Tables and Figures

Table 1: Association of Symptoms with Weight Gain

Caption: In the below model, age (as fractional polynomials, term1= $age^{-2} - 1.16$ and term2= $\ln(age) * age^{-2} - 0.08$), season (with sine/cosine terms), and an AR(1) covariance structure.

	Present in episode yes/no **change in weight (g) associated with symptom presence**	**duration** **change in weight (g) per days present**
Anorexia	-49.1 (-8.8, -9.9) (p=0.014)	-12.4 (-22.4, -2.4) (p=0.015)
Blood in Stool (observed by Mother)	-1.8 (-61.4, 57.8) (p=0.952)	-1.3 (-26.2,23.7) (p=0.920)
Blood in Stool (observed by lab tech)	10.6 (-72.5, 93.6) (p=0.803)	N/A
Fever	-46.9 (-88.1, -5.7) (p=0.026)	-17.4 (-33.4, -1.3) (p=0.034)
Nausea	-1.2 (-60.5, 58.2) (p=0.970)	-2.2 (-28.3, 23.8) (p=0.866)
Malaise	-49.4 (-84.9, -14.0) (p=0.006)	-9.5 (-17.8, -1.2) (p=0.025)

Mucus in Stool (observed by Mother)	-4.7 (-47.4, 38.0) (p=0.829)	0.1 (-14.4, 14.5) (p=0.994)
Mucus in Stool (observed by Lab tech)	0.3 (-34.4, 41.0) (p=0.863)	N/A
Stomach Pain	-13.9 (-48.8, 21.1) (p=0.427)	-5.4 (-13.3, 2.5) (p=0.179)
Vomiting	-56.9 (-109.2, -4.7) (p=0.033)	-23.2 (-46.0, -0.5) (p=0.046)
Four or more liquid stools in a 24/hr period	-44.0 (-80.6, -7.5) (p=0.018)	-23.6 (-37.6, -9.6) (p=0.001)
Maximum number of stools /24 hr period (continuous)	-9.9 (-18.0, -1.8) (p=0.016)	N/A
Episode Duration (per day - continuous)	-5.1 (-12.5, 2.4) (p=0.181)	N/A

Table 2: Correlations between symptoms retained in final severity score (N=3,738)

Symptoms are categorized according to the manner that they are included in the final score (0 days with symptom = 0, 1-2 days with symptom=1, 3-4 days with symptom=2, 5+ days with symptom=3).

	Anorexia	Fever	Vomiting	Liquid Stools	Max Stools
Days with Anorexia	1				
Days with Fever	0.27	1			
Days with Vomiting	0.24	0.24	1		
Days with >=4 Liquid Stools	0.32	0.25	0.16	1	
Maximum stools/24hr period	0.25	0.27	0.27	0.34	1

Table 3: Severity Scorecard

Symptom	Category	Points
Diarrhea	>=3 liquid or semi-liquid stools per day, for 1-13 days, with gaps of no more than one day	
Fever	No Fever	+0
	Fever for 1-2 days	+1
	Fever for 3-4 days	+2
	Fever for 5+ days	+3
Anorexia	No Anorexia	+0
	Anorexia for 1-2 days	+1
	Anorexia for 3-4 days	+2
	Anorexia for 5+ days	+3
Vomiting	No Vomiting	+0
	Vomiting for 1-2 days	+1
	Vomiting for 3-4 days	+2
	Vomiting for 5+ days	+3
Liquid Stools	No days with >=4 liquid stools	+0
	1-2 days with >=4 liquid stools	+1
	3-4 days with >=4 liquid stools	+2
	5+ days with >=4 liquid stools	+3
Maximum number of stools in a 24 hour period during the episode	3	+0
	4-5	+1
	6-7	+2
	>=8	+3
TOTAL		0-15

Table 4: Association between Severity Score and change in Weight and Weight-for-Height

The association between incident episodes of diarrheal classified as low (score 0-1), medium severity (score 2-7) and high severity (score >=8) on the change in weight and weight-for-height Z over 1-month intervals, is shown below. Age (same fractional polynomials as in symptom-specific models) and season (sine and cosine terms) were also adjusted for (beta coefficients not shown).

	1-month change in Weight (g)	1month change in WHZ (Z-score)
Low Severity	ref	ref
Medium Severity	-49.3 (-84.8, -13.8) (p=0.007)	-0.049 (-0.090, -0.008) (p=0.020)
High Severity	-133.0 (-223.2, -42.8) (p=0.004)	-0.180 (-285.2, -75.7) (p=0.001)

Table 5: Association between Severity Score and Linear Growth

The association between incident episodes of diarrheal classified as low (score 0-1), medium severity (score 2-7) and high severity (score >=8) on the change in height and HAZ over 9-month intervals, is shown below. Age (fractional polynomials used to adjust for age in the height model are term1= $age^{-2} - 0.56$ and term3= $\ln(age) * age^{3} - 2.41$), season (sine and cosine terms), stunting, and WHZ (categorized as >0, 0 to -1, and <-1) were also adjusted for (beta coefficients not shown). In the HAZ model, fractional polynomials for age are $age^{-2} - 1.80$ and = $\ln(age) * age^{2} - 0.53$.

	9mo change in Ht (cm)	9mo change in HAZ (Z-score)
Low-severity episodes (incidence)	-0.021 (-0.043, 0.001) (p=0.057)	-0.004 (-0.11, 0.003) (p=0.299)
Medium-severity episodes	-0.041(-0.065, -0.016) (p=0.001)	-0.010 (-0.19, -0.001) (p=0.022)
High-severity episodes	0.003 (-0.069, 0.074) (p=0.936)	-0.011 (-0.036,0.015) (p-0.423)
Episodes of dysentery	-0.113 (-0.189, -0.038) (p=0.003)	-0.034 (-0.062, -0.007) (p=0.013)

Figure 1: Conceptual Diagram of Idealized Severity Score

Figure 2: Example of Severity Score Applied to an Episode: A 6-day episode with fever on 3 days (+2), anorexia on 0 days (+0), vomiting on 1 day (+1), a maximum total number of stools/day of 6 (+2) and a total of 3 days with 4 or more liquid stools (+2) = total severity score of 7.

Figure 3: Distribution of Symptoms

Out of all episodes (n=3,738)

Figure 4: Histogram of severity score distribution. The y-axis (frequency) indicates the number of episodes assigned to the score (N= 3,738).

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract *The phrase 'Community-Based Studies' is used in the title, and 'cohort study' is used in the abstract to describe the study's design.*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found √
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported *Please see introduction.*
Objectives	3	State specific objectives, including any prespecified hypotheses *"the overall objective was to explore the association between common etiologies of diarrhea and early childhood growth. The work described here was a prespecificied secondary objective of the study."*
Methods		
Study design	4	Present key elements of study design early in the paper √
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection *Information about the period of recruitment, exposure, and follow-up are mentioned, however, they have been reported in greater detail in previous published reports.*
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Information about eligibility, sources, and methods of selection have been reported in detail in previous published reports.*
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed *N/A*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

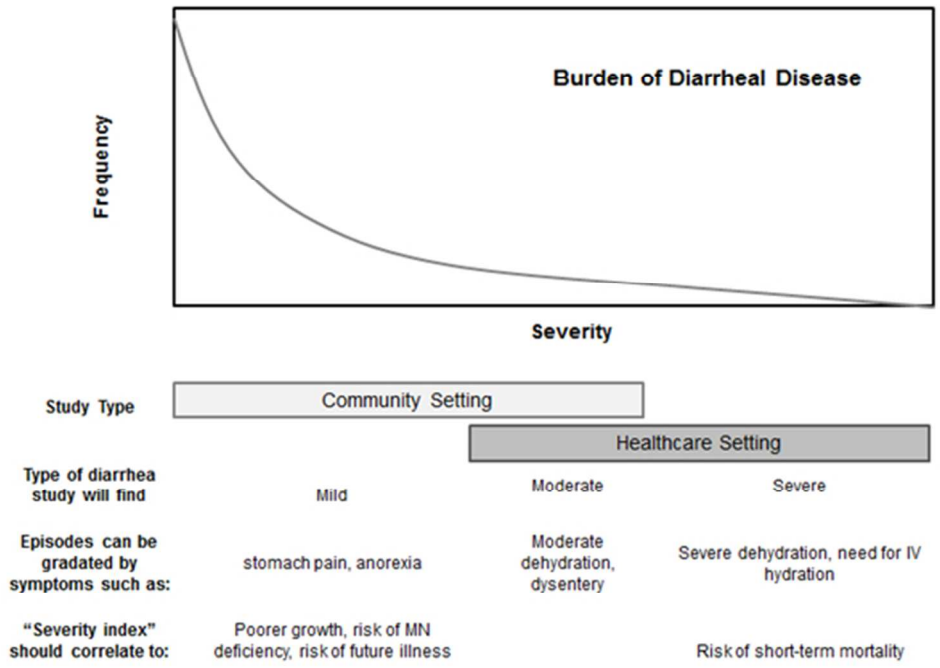
		√
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group √
Bias	9	Describe any efforts to address potential sources of bias *Attempts to avoid bias in the statistical analysis (sensitivity analysis) are described.*
Study size	10	Explain how the study size was arrived at *The original sample size was obtained based on the primary aim of estimating the association between enteropathogen-specific diarrheal episodes and growth.* *"A total of 3,738 acute episodes were available for analysis. Of these, 2,461 were used in building the severity score (on the basis of being associated with anthropometry according to the criteria above, and with duplicate episodes in the same month discounted)."*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why *Certain variables (symptoms) that went into the formation of a diarrheal severity score were grouped on the basis of high correlation (ρ>0.40); with only the variable that lead to the greatest improvement in model fit retained in the score.*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding *As described above, variables that were strongly correlated were not co-included in the formation of the described severity score. Since the outcome of interest was growth (weight and height velocity), age and season were accounted for as co-variates.*
		(*b*) Describe any methods used to examine subgroups and interactions *No subgroups were considered; mixed-effects models were used to account for correlation between episodes from the same child.*
		(*c*) Explain how missing data were addressed *The data relevant to this analysis was essentially complete.*
		(*d*) If applicable, explain how loss to follow-up was addressed

		Not highly applicable to this analysis
		(*e*) Describe any sensitivity analyses *Sensitivity analysis was performed to determine the effect of the omission of certain episodes on model outcomes, this is mentioned.*
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed *The number of total children is mentioned, greater details have been reported elsewhere.*
		(b) Give reasons for non-participation at each stage *Loss to follow up during the cohort was low, the breakdown of reasons for lost to follow up have been reported elsewhere.*
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders *This has been reported in great detail in other reports, and so we have chosen to limit the repetition of this data.*
		(b) Indicate number of participants with missing data for each variable of interest *N/A- missingness is negligible as the unit of analysis is the diarrheal episode, however, we are happy to include greater details in this report as well if it is desirable.*
		(c) Summarise follow-up time (eg, average and total amount) *This has been reported elsewhere. (In order to limit the length of the manuscript we have attempted not to duplicate previously reported information, especially as, in this report, the unit of analysis was the diarrheal episode, rather than the child. However, in all cases, we are happy to include greater details in this report as well if it is desirable.)*
Outcome data	15*	Report numbers of outcome events or summary measures over time *"A total of 3,738 acute episodes were available for analysis. Of these, 2,461 were used in building the severity score (on the basis of being associated with anthropometry according to the criteria above, and with duplicate episodes in the same month discounted)."*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included *In all instances, estimates were adjusted for age and seasonal effects.*
		(*b*) Report category boundaries when continuous variables were categorized √
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period *N/A*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses *These are reported.*
Discussion		
Key results	18	Summarise key results with reference to study objectives √
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias *Limitations of the study are discussed.*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence √
Generalisability	21	Discuss the generalisability (external validity) of the study results √
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based √

*Give information separately for exposed and unexposed groups.

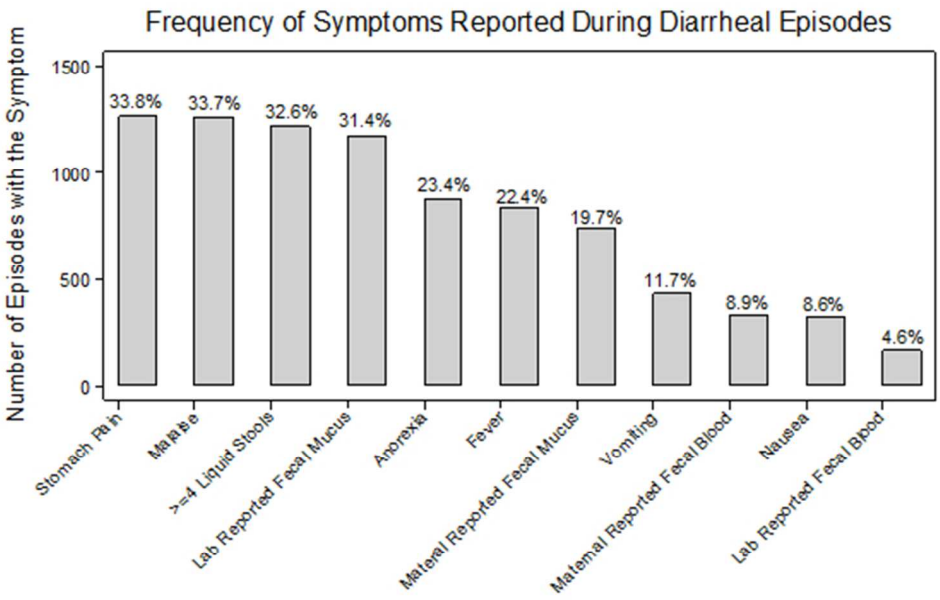
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.



Conceptual Diagram of Idealized Severity Score
165x119mm (96 x 96 DPI)

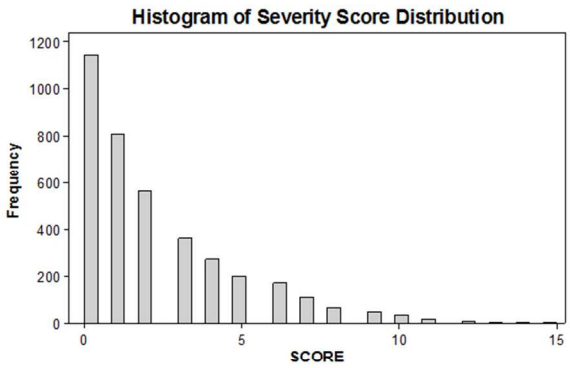
	Sun	Mon	Tues	Wed	Thurs	Fri	Sat
Fever	no	YES	YES	YES	no	no	no
Anorexia	no	no	no	no	no	no	no
Vomiting	no	no	YES	no	no	no	no
Total Number of stools	3	4	4	5	6	3	2
Total number of Liquid stools	0	0	4	4	4	0	0

Example of Severity Score Applied to an Episode: A 6-day episode with fever on 3 days (+2), anorexia on 0 days (+0), vomiting on 1 day (+1), a maximum total number of stools/day of 6 (+2) and a total of 3 days with 4 or more liquid stools (+2) = total severity score of 7.
209x78mm (96 x 96 DPI)



Distribution of Symptoms: Out of all episodes (n=3,738)

154x103mm (96 x 96 DPI)



Histogram of severity score distribution: The y-axis (frequency) indicates the number of episodes assigned to the score (N= 3,738).
254x142mm (96 x 96 DPI)

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An Instrument for the Assessment of Diarrheal Severity based on a Longitudinal Community-Based Study

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Title: An Instrument for the Assessment of Diarrheal Severity based on a Longitudinal Community-Based Study

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Abstract:

Objective Diarrhea is a significant contributer to morbidity and is among the leading causes of death of children living in poverty. As such, the incidence, duration, and severity of diarrheal episodes in the household are often key variables of interest in a variety of community-based studies. However, there currently exists no means of defining diarrheal severity that are: (a) specifically designed and adapted for community-based studies; (b) associated with poorer child outcomes; and (c) agreed upon by the majority of researchers. Clinical severity scores do exist and are used in health care settings, but these tend to focus on relatively moderate to severe dehydrating and dysenteric disease, require trained observation of the child, and, given the variability of access and utilization of health care, fail to sufficiently describe the spectrum of disease in the community setting.

Design Longitudinal cohort study

Setting Santa Clara de Nanay, a rural community in the Northern Peruvian Amazon

Participants 442 infants and children 0-72 months of age

Main Outcome Measures Change in weight over one month intervals and change in length/height over 9-month intervals

Results Diarrheal episodes with symptoms of fever, anorexia, vomiting, greater numbers of liquid stools per day, and greater number of total stools per day, were associated with poorer weight gain compared to episodes without these symptoms. An instrument to measure severity was constructed based upon the duration of these symptoms over the course of a diarrheal episode.

Conclusions In order to address limitations of existing diarrheal severity scores in the context of community-based studies, we propose an instrument comprised of diarrhea-associated symptoms easily measured by community health workers and based on the association of these symptoms with poorer child growth. This instrument can be used to test the impact of interventions on the burden of diarrheal disease.

Strengths and Limitations of the Study:

-Intensive (three-times weekly) surveillence was used to capture symptoms of diarrheal severity in a community-based context, and to relate these to weight gain.

-A lack of information about clinical signs associated with severe disease, including dehydration and rectal temperature, limit the comparability of this instrument to existing diarrheal severity scores.

Introduction

Diarrhea is common cause of morbidity and mortality among children in the developing world (1). In addition to causing an estimated 0.75 million deaths per year (2), is estimated that the average child under five in the developing world will experience 2.9 episodes per year (3). The severity of these episodes is a common factor of interest in community-based epidemiological studies designed to test the impact of an intervention and/or quantify the burden of diarrheal disease (4).

Within the context of community-based studies diarrhea is defined as three or more loose stools per 24-hour period (5), prolonged diarrhea is diarrhea lasting between 7-13 days, and 'persistent' diarrhea as an episode of at least 14 days (6,7). These definitions were standardized in the early 1990s, leading to greater comparability between studies, and progress in the field.

Definitions of diarrheal severity, however, have remained variable (4). Clinical indicators of severity such as dehydration and dysentery (8) are associated with an acute risk of patient mortality and are used to guide therapy. These symptoms, in addition to need for hospitalization can define moderate to severe diarrhea among cases presenting for care at a healthcare center, but will not gradate between the majority of mild to moderate cases in the community (see **Figure 1**). As diarrhea case fatality rates decline, there is increasing interest in understanding the impact of mild-to-moderate disease on child health and development. For these episodes, there is a need for non-clinical measurement instruments adapted for use at a community level.

Several severity measurement instruments have been developed for classifying rotavirus diarrhea (9–11). However, these scores were not designed to differentiate severity of non-rotavirus diarrhea, which is less frequently associated with symptoms such as vomiting. Although rotavirus is the most frequently isolated pathogen among hospitalized diarrhea cases, there are other pathogens that are isolated more frequently in a typical community context. Furthermore, instruments that include hospitalization as a model input are problematic in settings where access to inpatient care facilities is heterogeneous, as can be observed in many low and middle-income settings.

Previous instruments have included components such as rectal temperature and indexes of dehydration require either an invasive measurement or one that may be challenging to consistently measure across studies. These scales cannot be implemented in the context of community-based studies, where caregivers may not seek care for episodes of mild-to-moderate diarrhea and where surveillance is frequently bi-weekly or weekly (12) and many episodes resolve in the interval between a study worker's regularly scheduled visits. While some studies have attempted to correct this problem through the creation of "modified" Vesikari scores (13,14), these scores were based on data from Canadian infants and HIV+ infants, respectively, making their findings less generalizable to the typical cases of pediatric diarrhea in the developing world.

Finally, the determination of severity in the formation of these instruments has generally been based on the empiric distribution of characteristics such as fever or dysentery associated with that particular cohort, rather than through association with morbidity (4). There are currently no instruments that

correlate on the high end to severe outcomes such as mortality and hospitalization, and on the middle-to-low end with other, more frequently occurring adverse health outcomes.

Acute weight loss associated with a diarrheal episode puts a child at risk of becoming underweight and/or wasted, outcomes associated with an increased risk of mortality (15,16), further infectious disease (17) and future stunting (18). Poorer linear growth in early childhood is associated with long-term negative outcomes including poorer cognitive development (19), adult work capacity and income (20), and, for girls, poorer maternal heath (15). Therefore, short-term weight gain and medium-to-long term linear growth are appropriate functional outcomes through which to validate measures of disease severity, and symptoms associated with poorer growth should be prioritized in the formation of diarrheal severity scores.

Using data from a previously-established longitudinal cohort with a high incidence of diarrhea and stunting and with standard community-based active surveillance measures, we evaluated the impact of diarrheal-associated symptoms on short-term weight gain in the subsequent temporal period. From this, we formed a diarrheal severity score to predict acute weight loss as well as depressed linear growth over longer temporal windows. This instrument may be validated for use in community based studies, clinical trials, and water, sanitation, and hygiene interventions.

Methods

Data were from a prospective, community-based study of 442 children 0-72 months of age living in the community of Santa Clara, located 15 km southeast of Iquitos, Peru. The cohort and study design were described previously (21,22); the overall objective was to explore the association between common etiologies of diarrhea and early childhood growth. The work described here was a prespecified secondary objective of the study.

From October 2002 – April 2006, participating families were visited three-times weekly by a trained health promoter to document the number and consistency of stools passed by the child over the previous 24-hour period, as well as other symptoms such as fever, anorexia, malaise, nausea, vomiting, stomach pain, and the reported presence of blood and mucus in the child's feces. For example, malaise was translated as "malestar general" and described to mothers as a lack of energy or irritability in the child, and anorexia (translated as "recibe bien la comida") was described as the child's willingness/eagerness to eat as usual. This generated a continuous history of diarrheal disease over the surveillance period for each participating child. Anthropometry was collected monthly, and socioeconomic and demographic information were collected during two community censuses before and during the study period. Diarrhea was defined by three or more semi-liquid stools reported over a 24-hour period, with episodes separated by at least three symptom-free days. Stool samples were collected as soon as possible after the case definition for diarrhea was met, and not more than two days after the episode ended. Fecal blood and fecal mucus, as reported by a lab technician, were also reported once per episode.

Symptoms associated with diarrhea were defined as having occurred during the diarrheal episode, if they were present on any day of the episode. The duration of symptoms associated with diarrhea was defined as the number of days of the episode upon which the symptom occurred. Symptoms which were present the day before or the day after an episode of diarrhea were not counted.

Since persistent diarrhea is regarded as a separate epidemiological phenomenon with effects on growth apart from those of shorter episodes (23), only episodes of <14 days were retained in the analysis. In this cohort less than two percent of episodes were persistent (>=14 days = 2.4% of all episodes).

Statistical Methods

The percentages of episodes associated with a given symptom by age were tabulated and compared (ANOVA), and correlations and partial correlations between the presence of symptoms during an episode, and the duration of symptoms during an episode were calculated. All analysis was performed using Stata 11 & Stata 12 (Statacorp, College Station, TX, USA).

Effects of Specific Symptoms on short-term Weight Gain

The effect of the presence of a symptom (see list of symptoms in **Table 1**) on a child's weight gain was modeled using change in weight of the child before versus after the episode. Only intervals in which a diarrheal episode was present were include in the model (i.e. episodes of diarrhea were compared to each other, and were not compared with periods in which no diarrhea occurred). Only episodes that occurred between two instances of anthropometry one month apart were considered, i.e., episodes which overlapped an anthropometric measurement were discounted. In order to avoid instances in which acute dehydration might have impacted weight gain, episodes that ended less than two days before anthropometry were also excluded. Rather than include the same one-month interval of anthropometry repeatedly within the model, when more than one episode occurred within the same one month interval, only the episode of longer duration was retained, and the total number of episodes in the month was considered as a covariate in the analysis. Sensitivity analysis was performed to determine the effect of these omissions on model outputs.

$$Wt_{ij} - Wt_{i-1,j} = b_j + \beta_0 + \beta_1 D_{symptom} + \beta_2 \sin_{season} + \beta_3 \cos_{season} + \ldots$$
$$+ \beta_4 Age\ \ Term\ \ 1 + \beta_5 Age\ \ Term\ \ 2 + \varepsilon_{ij} \quad \textbf{(Equation 1).}$$

The final model used to evaluate associations of symptoms with weight gain is shown in equation 1. $D_{symptom}$ represents the presence or absence of a symptom during the episode or the duration (in days) of the symptom during an episode (Column 2 of **Table 1**). Seasonal variation in weight gain was modeled by adding the terms $sine(\frac{2d\pi}{t})$ and $cosine(\frac{2d\pi}{t})$, where d is the day of the year, and t is 365 (24). Age Term 1 and Age Term 2 are fractional polynomials used to estimate the impact of age on monthly weight gain. The models were also fitted with a child-level random intercept and a covariance

structure that fixed a first-order autoregressive residual structure to account for those instances in which a child experienced episodes of diarrhea over consecutive one-month intervals.

Formation of a Severity Score

Symptoms negatively associated with weight gain were categorized by duration and combined to form a severity score. In order to judge how many points should be given to symptoms of a given duration, models where duration was categorical were used to determine whether the association per day of the symptom on weight gain was additive, or whether there were threshold effects. After forming the score, sensitivity analysis was used to check that the inclusion of each additional component improved the overall model fit.

The score was then collapsed into three categories representing relatively mild, moderate, and severe diarrhea. The same model was then fit using the categorized variable. The unadjusted mean change in weight and weight for height Z score (WHZ) by severity category, and the adjusted one-month change in WHZ by severity category, were also estimated.

Effects of Specific Symptoms and Overall Severity on Linear Growth

In order to examine the relationship between individual symptoms and change in length/height, the cumulative incidence of episodes with and without each symptom was summed over nine-month intervals, and the effect of these episodes on linear growth (change in length/height) was modeled using the equation in Equation 2, where $D_{symptom\_present}$ is the cumulative incidence of diarrheal episodes in which the symptom occurred, and $D_{symptom\_absent}$ is the cumulative incidence of diarrheal episodes in which the symptom was absent, during the nine-month interval. The same seasonal terms and a set of fractional polynomial terms generated separately from those in the weight model were included. The models were also fitted with a child-level random intercept and a covariance structure that fixed a first-order autoregressive residual structure.

$$Ht_{ij} - Ht_{i-9,j} = b_j + \beta_0 + \beta_1 D_{symptom\_present} + \beta_2 D_{symptom\_absent} + \beta_3 \sin_{season} + \beta_4 \cos_{season} + \beta_5 AgeTerm\_1 + \beta_6 AgeTerm\_2 + \varepsilon_{ij}$$

(Equation 2).

The impact of episodes of varying severity, as categorized by the severity score developed above, was then tested similarly, using a model with three incidence terms, D_{mild}, $D_{moderate}$, and D_{severe}, representing the cumulative incidence of mild, moderate, and severe episodes in the nine-month interval, respectively. A similar model using nine-month change in HAZ as an outcome was used to test the effects of disease severity on HAZ.

Results

A total of 3,915 acute episodes were available for analysis. Of these, 2,462 were used in building the severity score (on the basis of being associated with anthropometry according to the criteria above, and with shorter episodes in the same month discounted) (see **Figure 2**). Sensitivity analysis did not reveal any bias introduced by removing these episodes. Overall, 93.2% of the non-persistent episodes were associated with a lab result, of which 96.6% were collected within two days of the onset of the episode.

The symptoms considered in the analysis are reported in **Table 1**. The number of episodes associated with each symptom is shown in **Figure 3**. Most symptoms (all except anorexia and dysentery), were most common among the youngest children (<=2 years) and decreased in prevalence with age.

Correlations between the reporting of these symptoms during an episode ranged 0.02 to 0.64. The strongest correlations were between maternal report of blood and lab-reported blood (rho=0.64), followed by nausea and vomiting (rho=0.64), total depositions and liquid depositions >=4 (rho=0.59), maternal report of blood and maternal report of mucus (rho=0.59), malaise and stomach pain (rho=0.55), and malaise and anorexia (rho=0.43). The correlations between the symptoms as categorized in the final severity score are reported below (**Table 2**).

Effects of Specific Symptoms on short-term Weight Gain

Anorexia, fever, malaise, vomiting and the maximum number of stools per 24/hour period, were all associated with poorer weight gain in months associated with diarrhea (p<=0.010). These symptoms were associated with between 9.9 and 28.0 grams less weight gain per each day in the episode during which they occurred (**Table 1**).

The number of days in an episode with>=2, >=4, >=6, and >=8 liquid and or/semi-liquid stools were strongly correlated with each other. Of these, the number of days with >=4 liquid stools led to the greatest improvement in model fit and was therefore retained for further analysis. Each day in which >=4 liquid stools were present was associated with 23.5 grams less weight gain **(Table 1**).

Formation of a Severity Score

In total, six factors associated with poorer weight gain. With the exception of malaise, these variables were then categorized into 4 levels according to the duration of the symptom (**Table 3**), and the severity score was built by summing these five categorical variables **(Table 3, Figure 4** and **Supplemental Table 1)**. In order to make the score more parsimonious, malaise was excluded while anorexia, which was correlated with malaise (rho=0.43), appeared in multivariate models to explain the association between malaise and weight gain, and was also perceived as less subjective, was retained. Other symptoms were more weakly correlated with each other (rho <0.40) (**Table 2**), and the exclusion of any one from the overall score led to a decrease in model fit. A model that included the overall score also fit better than one in which all variables were included individually.

Episodes were categorized empirically based on their distribution within this dataset as mild (score= 0, no additional symptoms present beyond meeting the minimum criteria for diarrhea), moderate (1-6 (35^{th}-95^{th} percentile) and severe (>=7) (>95^{th} percentile). Using this categorization process, episodes of

moderate severity were did not predict less weight gain over one month than episodes of mild severity (-25.4g, p=0.186), and episodes of high severity predicted 132.2 g less weight gain (**Table 4**). When change in WHZ was used as outcome, moderate and severe episodes predicted a loss of 0.008 (p=0.720) and 0.171 (p=<0.001) Z-scores over the month of the episode, respectively (**Table 4**).

Effects of Specific Symptoms and Overall Severity on Linear Growth

Of all the symptoms tested, only dysentery, as defined by laboratory-observed blood in stool, was independently predictive of poorer linear growth (results not shown). Because dysentery was not included in the severity score, it was then added as an independent variable to the model testing the impact of the severity score overall.

Incident episodes of low severity were not associated with poorer linear growth or changes in HAZ, while each episode of moderate severity predicted 0.035cm less linear growth and 0.009 less in HAZ. Episodes of the highest severity were also unassociated with changes in linear growth and HAZ over the 9 month period (**Table 5**).

Discussion

During diarrheal episodes, anorexia/malaise, fever, vomiting, the number of days with >=4 liquid stools, and the maximum number of depositions per 24/hour period, were the symptoms most strongly associated with poorer weight gain. This suggests the prioritization of these symptoms in the formation of a severity score to characterize mild-to-moderate diarrhea in community-based study settings.

Several symptoms of potential interest were not collected and therefore could not be included in our analysis, limiting our ability to compare our severity score to that of the 20-point Ruuska and Vesikari score (11), the 24-point instrument proposed by Clark (9), or the index proposed by Ericsson and subsequently adapted by Jacobs et al (25–27). The symptoms that were not collected are those which require measurement or assessment of the child by a trained health worker, i.e. rectal temperature and dehydration. Additionally, the maximum number of emeses in a 24-hour period was not noted. Our final severity score, which is based exclusively on information extracted from the verbal report of a caregiver during three-times weekly visits, is similar to the Vesakari and Clark scores, with the addition of anorexia and the number of days with four or more liquid stools, and minus those components that depend on trained observation, on the level of healthcare received (outpatient, hospitalization, etc.), or on treatment decisions made by a health care professional during the episode (e.g. intravenous rehydration therapy required yes/no) (Supplemental Table 1).

For these reasons, our score may have greater utility than existing severity indices in a variety of community-based study designs where daily clinical assessments are not realistic. However, an ability to compare our score to observations made in a clinical setting would be of methodological value (28), particularly as symptoms based on maternal report are relatively subjective (although more severe symptoms do tend to be more reliably reported (29)). A severity score that includes clinical observations

but could also be harmonized with a simplified version based on caregiver reported symptoms, and/or objective measures that can be used in a community-based setting, is also desirable. The association between severity and the risk of hospitalization should also be considered and assessed in a variety of settings (30,31), but because hospitalization and treatment are dependent upon access and not purely clinical need, these are better considered as outcomes that may be associated with diarrheal severity rather than components of diarrheal severity in and of themselves.

Another weakness of our study was a relatively large number of "mild" episodes with a severity score of 0, and the relatively small number of "severe" episodes with a severity score of 7 or above. Many episodes were of one or two days in duration, associated with a low (3 or 4) number of maximum stools per 24 hour period, and, although they met epidemiological criteria for diarrhea, no others symptoms that might suggest systemic involvement were present. In contrast, episodes required the presence of at least three symptoms to be scored as 'severe' (defined here as approximately the 95th percentile). These observations are consistent with the best available estimates of the proportion of categorization in mild, moderate, and severe episodes in the community setting (7). In the "severe" category, there was a trend towards episodes of higher scores being associated with greater weight loss, i.e. an episode of severity score 15 had a greater impact than one of severity 8 (result not shown). However, because the number of episodes of greater severity was small, they were grouped in a single category. The estimated association between severe episodes and weight gain and linear growth is also correspondingly less precise. While other categorizations of each symptom within the overall score were considered, including categorizations that resulted in a greater proportion of episodes having higher scores, these were less strongly associated with weight gain than the one we present here.

In this index, we assess duration of symptoms differently than previous scores. Both the Vesikari and Clark indexes include the possibility of less than three maximum number of stools/day, which conflicts with the widely accepted definition of diarrhea in a community-based setting as requiring a minimum of three liquid or semi-liquid stools (**Supplemental Table 2**). We defined the bounds of an episode according to the standard epidemiological definition, and then calculated the duration of each symptom under that assumption. Instead of episode duration being included as a separate component, it was only included indirectly, through the duration of days in which each symptom was present. We believe this is important in evaluating enteric disease caused by a range of both invasive and non-invasive pathogens where the illness syndrome is diverse. In contrast, previous severity scores have been built around the ability of a symptom to discriminate between pathogens: for instance, rotavirus diarrhea is typically associated with significant vomiting and frequent stools, but relatively less fever, and the Vesakari index gives purging frequency and duration a high weight accordingly[1]. Unfortunately, although common bacterial enteropathogens (ETEC, *Shigella,* and *Campylobacter)* were screened for in this study (21,32), rotavirus was not, and so, while validation of this scoring system against the Vesikari score would be of particular interest, we are unable to do so in this study.

We also included in our score the total number of days with four or more liquid stools. The number of total liquid + semi-liquid stools, and the number of days with >=4 liquid+semi-liquid stools were strongly

[1] With a maximum of 6 points related to vomiting and a maximum of 3 related to fever.

correlated with the maximum number of stools/24 hour period, while the number of days with >=4 liquid stools was relatively less correlated with the total or maximum number of stools and was strongly associated with poorer weight gain even after adjusting for total stools.

Dysentery, as defined by caregiver-reported or laboratory technician reported visible blood, was not found to be a predictor of immediate episode-associated weight loss. However, it was independently predictive of poorer linear growth, a finding in agreement with other reports (33). The prevention of dysenteric diarrhea, which is associated with progression to persistent diarrheal (23) and mortality (34) and merits prioritization. The importance of dysentery as a cause of linear growth faltering but not acute weight loss also suggests that multiple measurement tools for diarrheal severity may be useful. In addition to acute weight loss and linear growth, which we used here, factors such the likelihood of further infectious disease, the risk of acute dehydration (8), and the risk of mortality are important child health outcomes that should be considered in score-building (**Figure 1**).

Standardized and carefully considered measures of diarrheal severity are desirable in clinical trials, intervention studies and descriptive community-based studies of diarrhea in the low-income settings (35), and would improve understanding of the impact of disease control measures on morbidity burden. The severity score we derived here is composed of simple components and allows for the meaningful classification of a diarrheal disease episode based upon the most common adverse events associated with diarrhea; depressed weight gain and poorer linear growth, an improvement over earlier scores built empirically around symptom frequency. The collection of the input data for this score is highly feasible and are likely available in many extant datasets; further validation could improve the estimates of diarrhea severity and disease burden across epidemiologic settings.

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Contributors

MK conceived and designed the study. MK, MPO, PPY designed the data collection tools, monitored recruitment and data collection for the study, and supervised the study. PPY managed and cleaned the data. GL designed and implemented the analysis, CFW, LEC, REB, and DAS provided guidance during the analysis, and contributed to the interpretation of data. All authors helped write and critically review the article, and all authors have approved the final version to be published and agree to be accountable for all aspects of the work. MK and GL are the guarantors.

Competing Interests

We have read and understood the BMJ policy on declaration of interests and declare the following interests: None. All authors have completed the ICMJE uniform disclosure form at www.icjme.org/coi_disclosure.pdf (available on request from the corresponding author).

Data sharing

Raw data used in the analysis is available on request from the corresponding author at mkosek@jhsph.edu. Statistical code is also available upon request.

Ethical Approval

This study was approved by the Institutional Review boards of the Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (IRB H.22.01.01.02.A), the US Naval Medical Research Center, Silver Springs, MD (IRB NMRCD.2002.0009), and Asociación Benéfica PRISMA, Lima, Peru (no IRB number). All participating families gave signed, informed consent before taking part in the study.

Declaration of Transparency

Gwenyth Lee confirms that this article is an honest, accurate and transparent account of the study reported, that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Tables and Figures

Table 1: Association of Symptoms with Weight Gain

Caption: In the below model, age (as fractional polynomials, term1= $age^{-2} - 1.16$ and term2= $\ln(age) * age^{-2} - 0.08$), season (with sine/cosine terms), and an AR(1) covariance structure.

	Present in episode yes/no change in weight (g) associated with symptom presence	duration change in weight (g) per days present
Anorexia	-46.6 (-87.7, -5.6) (p=0.026)	-12.9 (-23.1, -2.7) (p=0.013)
Blood in Stool (observed by Mother)	-2.1 (-61.7, 57.5) (p=0.946)	-4.1 (-30.1,21.9) (p=0.757)
Blood in Stool (observed by lab tech)	10.3 (-72.8, 93.5) (p=0.807)	N/A
Fever	-47.9 (-89.1, -6.5) (p=0.023)	-19.5 (-36.7, -2.3) (p=0.026)
Nausea	-1.5 (-60.8, 57.9) (p=0.962)	-2.2 (-29.6, 25.2) (p=0.875)
Malaise	-49.5 (-85.0, -14.1) (p=0.006)	-9.9 (-18.3, -0.4) (p=0.022)
Mucus in Stool (observed by Mother)	-4.5 (-47.3, 38.3) (p=0.837)	-0.1 (-15.0, 15.0) (p=0.998)
Mucus in Stool (observed by Lab tech)	2.9 (-34.8, 40.6) (p=0.879)	N/A
Stomach Pain	-13.9 (-48.9, 21.0) (p=0.435)	-5.8 (-13.7, 2.2) (p=0.156)
Vomiting	-57.0 (-109.3, -4.7) (p=0.033)	-28.0 (-52.9, 30.8) (p=0.028)
Four or more liquid stools in a 24/hr period	-43.1 (-79.6, -6.6) (p=0.021)	-23.5 (-37.5, -9.5) (p=0.001)
Maximum number of stools /24 hr period (continuous)	-9.9 (-18.0, -1.8) (p=0.016)	N/A
Episode Duration (per day - continuous)	-5.1 (-12.5, 2.4) (p=0.181)	N/A

Table 2: Correlations between symptoms retained in final severity score (N=3,915)

Symptoms are categorized here according to the manner that they are included in the final score (0 days with symptom = 0, 1-2 days with symptom=1, 3-4 days with symptom=2, 5+ days with symptom=3).

	Anorexia	Fever	Vomiting	Liquid Stools	Max Stools
Days with Anorexia	1				
Days with Fever	0.24	1			
Days with Vomiting	0.23	0.30	1		
Days with >=4 Liquid Stools	0.24	0.27	0.29	1	
Maximum stools/24hr period	0.32	0.29	0.30	0.38	1

Table 3: Severity Scorecard

Symptom	Category	Points
Diarrhea	>=3 liquid or semi-liquid stools per day, for 1-13 days, with gaps of no more than two days	
Fever	No Fever	+0
	Fever for 1-2 days	+1
	Fever for 3-4 days	+2
	Fever for 5+ days	+3
Anorexia	No Anorexia	+0
	Anorexia for 1-2 days	+1
	Anorexia for 3-4 days	+2
	Anorexia for 5+ days	+3
Vomiting	No Vomiting	+0
	Vomiting for 1-2 days	+1
	Vomiting for 3-4 days	+2
	Vomiting for 5+ days	+3
Liquid Stools	No days with >=4 liquid stools	+0
	1-2 days with >=4 liquid stools	+1
	3-4 days with >=4 liquid stools	+2
	5+ days with >=4 liquid stools	+3
Maximum number of stools in a 24 hour period during the episode	3	+0
	4-5	+1
	6-7	+2
	>=8	+3
TOTAL		0-15

Table 4: Association between Severity Score and change in Weight and Weight-for-Height

The association between incident episodes of diarrheal classified as low (score 0), medium severity (score 1-6) and high severity (score >=7) on the change in weight and weight-for-height Z over 1-month intervals, is shown below. Age (same fractional polynomials as in symptom-specific models) and season (sine and cosine terms) were also adjusted for (beta coefficients not shown).

	1-month change in Weight (g)	1month change in WHZ (Z-score)
Low Severity	ref	ref
Medium Severity	-25.4 (-63.0, 12.2) (p=0.186)	-0.008 (-0.052, 0.036) (p=0.720)
High Severity	-132.2 (-213.6, -50.7) (p=0.001)	-0.171 (-0.266, -0.077) (p<0.001)

Table 5: Association between Severity Score and Linear Growth

The association between incident episodes of diarrheal classified as low (score 0), medium severity (score 1-6) and high severity (score >=7) on the change in height and HAZ over 9-month intervals, is shown below. Age (fractional polynomials used to adjust for age in the height model are term1= $age^{-2} - 0.56$ and term3= $\ln(age) * age^{3} - 2.41$), season (sine and cosine terms), stunting, and WHZ (categorized as >0, 0 to -1, and <-1) were also adjusted for (beta coefficients not shown). In the HAZ model, fractional polynomials for age are $age^{-2} - 1.80$ and $\ln(age) * age^{2} - 0.53$.

	9mo change in Ht (cm)	9mo change in HAZ (Z-score)
Low-severity episodes (incidence)	-0.014 (-0.042, 0.015) (p=0.348)	-0.001 (-0.012, 0.009) (p=0.755)
Medium-severity episodes	-0.035 (-0.056, -0.014) (p=0.001)	-0.009 (-0.016, -0.001) (p=0.025)
High-severity episodes	-0.011 (-0.067, 0.044) (p=0.690)	-0.008 (-0.028, 0.012) (p=0.439)
Episodes of dysentery	-0.112 (-0.189, -0.036) (p=0.004)	-0.033 (-0.061, -0.006) (p=0.018)

Figure 1: Conceptual Diagram of Idealized Severity Score

Figure 2: Episodes included in the analysis

Figure 3: Distribution of Symptoms: Out of all episodes (n=3,915)

Figure 4: Histogram of severity score distribution: The y-axis (frequency) indicates the number of episodes assigned to the score (N= 3,915).

Title: An Instrument for the Assessment of Diarrheal Severity ~~in~~based on a Longitudinal Community-Based ~~Studies~~Study

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Abstract:

Objective Diarrhea is a significant contributer to morbidity and is among the leading causes of death of children living in poverty. As such, the incidence, duration, and severity of diarrheal episodes in the household are often key variables of interest in a variety of community-based studies. However, there currently exists no means of defining diarrheal severity that are: (a) specifically designed and adapted for community-based studies; (b) associated with poorer child outcomes; and (c) agreed upon by the majority of researchers. Clinical severity scores do exist and are used in health care settings, but these tend to focus on relatively moderate to severe dehydrating and dysenteric disease, require trained observation of the child, and, given the variability of access and utilization of health care, fail to sufficiently describe the spectrum of disease in the community setting.

Design Longitudinal cohort study

Setting Santa Clara de Nanay, a rural community in the Northern Peruvian Amazon

Participants 442 infants and children 0-72 months of age

Main Outcome Measures Change in weight over one month intervals and change in length/height over 9-month intervals

Results Diarrheal episodes with symptoms of fever, anorexia, vomiting, greater numbers of liquid stools per day, and greater number of total stools per day, were associated with poorer weight gain compared to episodes without these symptoms. An instrument to measure severity was constructed based upon the duration of these symptoms over the course of a diarrheal episode.

Conclusions In order to address limitations of existing diarrheal severity scores in the context of community-based studies, we propose an instrument comprised of diarrhea-associated symptoms easily measured by community health workers and based on the association of these symptoms with poorer child growth. This instrument can be used to test the impact of interventions on the burden of diarrheal disease ~~severity~~.

Strengths and Limitations of the Study:

-Intensive (three-times weekly) surveillance was used to capture symptoms of diarrheal severity in a community-based context, and to relate these to weight gain.

~~Symptoms~~ A lack of information about clinical signs associated with severe disease, including dehydration and rectal temperature, limit the comparability of this instrument to existing diarrheal severity scores.

Introduction

~~Diarrhea is common cause of morbidity and mortality among children in the developing world (1). In addition to causing an estimated 0.75 million deaths per year (2), is estimated that the average child under five in the developing world will experience 2.9 episodes per year (3). The severity of these episodes is a common factor of interest in community-based epidemiological studies designed to test the impact of an intervention and/or quantify the burden of diarrheal disease (4).~~

~~Within the context of community-based studies diarrhea is defined as three or more loose stools per 24-hour period (5), prolonged diarrhea is diarrhea lasting between 7-13 days, and 'persistent' diarrhea as an episode of at least 14 days (6,7). These definitions were standardized in the early 1990s, leading to greater comparability between studies, and progress in the field.~~

Diarrhea is common cause of morbidity and mortality among children in the developing world (1). In addition to causing an estimated 0.75 million deaths per year (2), is estimated that the average child under five in the developing world will experience 2.9 episodes per year (3). The severity of these episodes is a common factor of interest in community-based epidemiological studies designed to test the impact of an intervention and/or quantify the burden of diarrheal disease (4).

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Definitions of diarrheal severity, however, have remained variable ~~(4). Clinical indicators of severity such as dehydration and dysentery (8)~~(4). Clinical indicators of severity such as dehydration and dysentery (8) are associated with an acute risk of patient mortality and are used to guide therapy. These symptoms, in addition to need for hospitalization can define moderate to severe diarrhea among cases presenting for care at a healthcare center, but will not gradate between the majority of mild to moderate cases in the community (see **Figure 1**). As diarrhea case fatality rates decline, there is increasing interest in understanding the impact of mild-to-moderate disease on child health and development. For these episodes, there is a need for non-clinical measurement instruments adapted for use at a community level.

~~Several severity measurement instruments have been developed for classifying rotavirus diarrhea (9–11). However, these scores were not designed to differentiate severity of non-rotavirus diarrhea, which is less frequently associated with symptoms such as vomiting. Although rotavirus is the most frequently isolated pathogen among hospitalized diarrhea cases, there are other pathogens that are isolated more frequently in a typical community context. Furthermore, instruments that include hospitalization as a~~

~~model input are problematic in settings where access to inpatient care facilities is heterogeneous, as can be observed in many low and middle-income settings.~~

~~Previous instruments included components such as rectal temperature and indexes of dehydration require either an invasive measurement or one that may be challenging to consistently measure across studies. These scales cannot be implemented in the context of community-based studies, where caregivers may not seek care for episodes of mild-to-moderate diarrhea and where surveillance is frequently bi-weekly or even weekly (12) and many episodes resolve in the interval between a study worker's regularly scheduled visits. While some studies have attempted to correct this problem through the creation of "modified" Vesikari scores (13,14), these scores were based on data from Canadian infants and HIV+ infants, respectively, making their findings less generalizable to the typical cases of pediatric diarrhea in the developing world.~~

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Finally, the determination of severity in the formation of these instruments has generally been based on the empiric distribution of characteristics such as fever or dysentery associated with that particular cohort, rather than through association with morbidity ~~(4).~~(4). There are currently no instruments that correlate on the high end to severe outcomes such as mortality and hospitalization, and on the middle-to-low end with other, more frequently occurring adverse health outcomes.

~~Acute weight loss associated with a diarrheal episode puts a child at risk of becoming underweight and/or wasted, outcomes associated with an increased risk of mortality (15,16), further infectious disease (17) and future stunting (18). Poorer linear growth in early childhood is associated with long-term negative outcomes including poorer cognitive development (19), adult work capacity and income (20), and, for girls, poorer maternal heath (15). Therefore, short-term weight gain and medium-to-long term linear growth are appropriate functional outcomes through which to validate measures of disease~~

~~severity, and symptoms associated with poorer growth should be prioritized in the formation of diarrheal severity scores.~~

~~Using data from a previously-established longitudinal cohort with a high incidence of diarrhea and stunting and with standard community-based active surveillance measures, we evaluated the impact of diarrheal-associated symptoms on short-term weight gain in the subsequent temporal period. From this, we formed a diarrheal severity score to predict acute weight loss as well as depressed linear growth over longer temporal windows. This instrument may be validated for use in community based studies, clinical trials, and water, sanitation, and hygiene interventions.~~

~~**Methods**~~

~~Data were from a prospective, community-based study of 442 children 0-72 months of age living in the community of Santa Clara, located 15 km southeast of Iquitos, Peru. The cohort and study design were described previously (21,22); the overall objective was to explore the association between common etiologies of diarrhea and early childhood growth. The work described here was a prespecified secondary objective of the study.~~

~~From October 2002 – April 2006, participating families were visited three-times weekly by a trained health promoter to document the number and consistency of stools passed by the child over the previous 24-hour period, as well as other symptoms such as fever, anorexia, malaise, nausea, vomiting, stomach pain, and the reported presence of blood and mucus in the child's feces.~~ Acute weight loss associated with a diarrheal episode puts a child at risk of becoming underweight and/or wasted, outcomes associated with an increased risk of mortality (15,16), further infectious disease (17) and future stunting (18). Poorer linear growth in early childhood is associated with long-term negative outcomes including poorer cognitive development (19), adult work capacity and income (20), and, for girls, poorer maternal heath (15). Therefore, short-term weight gain and medium-to-long term linear growth are appropriate functional outcomes through which to validate measures of disease severity, and symptoms associated with poorer growth should be prioritized in the formation of diarrheal severity scores.

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Symptoms associated with diarrhea were defined as having occurred during the diarrheal episode, if they were present on any day of the episode. The duration of symptoms associated with diarrhea was defined as the number of days of the episode upon which the symptom occurred. Symptoms which were present the day before or the day after an episode of diarrhea were not counted.

Since persistent diarrhea is regarded as a separate epidemiological phenomenon with effects on growth apart from those of shorter episodes~~(23),~~ (23), only episodes of <14 days were retained in the analysis. In this cohort less than two percent of episodes were persistent (>=14 days = ~~1.5~~2.4% of all episodes).

Statistical Methods

The percentages of episodes associated with a given symptom by age were tabulated and compared (ANOVA), and correlations and partial correlations between the presence of symptoms during an episode, and the duration of symptoms during an episode were calculated. All analysis was performed using Stata 11 & Stata 12 (Statacorp, College Station, TX, USA).

Effects of Specific Symptoms on short-term Weight Gain

The effect of the presence of a symptom (see list of symptoms in **Table 1**) on a child's weight gain was modeled using change in weight of the child before versus after the episode. Only intervals in which a diarrheal episode was present were include in the model (i.e. episodes of diarrhea were compared to

each other, and were not compared with periods in which no diarrhea occurred). Only episodes that occurred between two instances of anthropometry one month apart were considered, i.e., episodes which overlapped an anthropometric measurement were discounted. In order to avoid instances in which acute dehydration might have impacted weight gain, episodes that ended less than two days before anthropometry were also excluded. ~~When~~Rather than include the same one-month interval of anthropometry repeatedly within the model, when more than one episode occurred within the same one month interval, only the episode of longer duration was retained ~~in the model~~, and the total number of episodes in the month was considered as a covariate in the analysis. Sensitivity analysis was performed to determine the effect of these omissions on model outputs.

$$Wt_{ij} - Wt_{i-1,j} = b_j + \beta_0 + \beta_1 D_{symptom} + \beta_2 \sin_{season} + \beta_3 \cos_{season} + \ldots + \beta_4 Age\ \ Term\ \ 1 + \beta_5 Age\ \ Term\ \ 2 + \varepsilon_{ij}$$

$$Wt_{ij} - Wt_{i-1,j} = b_j + \beta_0 + \beta_1 D_{symptom} + \beta_2 \sin_{season} + \beta_3 \cos_{season} + \ldots + \beta_4 Age\ \ Term\ \ 1 + \beta_5 Age\ \ Term\ \ 2 + \varepsilon_{ij}$$

(Equation 1).

The final model used to evaluate associations of symptoms with weight gain is shown in equation 1. ~~$D_{symptom}$~~ $D_{symptom}$ represents the presence or absence of a symptom during the episode or the duration~~,~~ (in days~~,~~) of the symptom during an episode (Column 2 of **Table ~~3~~1**). Seasonal variation in weight gain was modeled by adding the terms $sine(\frac{2d\pi}{t})$ and $cosine(\frac{2d\pi}{t})$, where d is the day of the year, and t is 365 ~~(24).~~ (24). Age Term 1 and Age Term 2 are fractional polynomials used to estimate the impact of age on monthly weight gain. The models were also fitted with a child-level random intercept and a covariance structure that fixed a first-order autoregressive residual structure to account for those instances in which a child experienced episodes of diarrhea over consecutive one-month intervals.

Formation of a Severity Score

Symptoms negatively associated with weight gain were categorized by duration and combined to form a severity score. ~~When several symptoms were strongly correlated (rho>0.40), only the symptom that improved model fit was included in the severity score.~~In order to judge how many points should be given to symptoms of a given duration, models where duration was categorical were used to determine whether the association per day of the symptom on weight gain was additive, or whether there were threshold effects. After forming the score, sensitivity analysis was used to check that the inclusion of each additional component improved the overall model fit.

~~This~~The score was then collapsed into three categories representing relatively mild, moderate, and severe diarrhea. The same model was then fit using the categorized variable. The unadjusted mean change in weight and weight for height Z score (WHZ) by severity category, and the adjusted one-month change in WHZ by severity category, were also estimated.

Effects of Specific Symptoms and Overall Severity on Linear Growth

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In order to examine the relationship between individual symptoms and change in length/height, the cumulative incidence of episodes with and without each symptom was summed over nine-month intervals, and the effect of these episodes on linear growth (change in length/height) was modeled using the equation in Equation 2, where ~~$D_{symptom\_present}$~~ $D_{symptom\_present}$ is the cumulative incidence of diarrheal episodes in which the symptom occurred, and ~~$D_{symptom\_absent}$~~ $D_{symptom\_absent}$ is the cumulative incidence of diarrheal episodes in which the symptom was absent, during the nine-month interval. The same seasonal terms and a set of fractional polynomial terms generated separately from those in the weight model were included. The models were also fitted with a child-level random intercept and a covariance structure that fixed a first-order autoregressive residual structure.

~~$$Ht_{ij} - Ht_{i-9,j} = b_j + \beta_0 + \beta_1 D_{symptom\_present} + \beta_2 D_{symptom\_absent} + \beta_3 \sin_{season} + \beta_4 \cos_{season} + \beta_5 AgeTerm\_1 + \beta_6 AgeTerm\_2 + \varepsilon_{ij}$$~~

$$Ht_{ij} - Ht_{i-9,j} = b_j + \beta_0 + \beta_1 D_{symptom\_present} + \beta_2 D_{symptom\_absent} + \beta_3 \sin_{season} + \beta_4 \cos_{season} + \beta_5 AgeTerm\_1 + \beta_6 AgeTerm\_2 + \varepsilon_{ij}$$

(Equation 2).

The impact of episodes of varying severity, as categorized by the severity score developed above, was then tested similarly, using a model with three incidence terms, ~~D_{mild}~~, ~~$D_{moderate}$~~, and ~~D_{severe}~~ D_{mild}, $D_{moderate}$, and D_{severe}, representing the cumulative incidence of mild, moderate, and severe episodes in the nine-month interval, respectively. A similar model using nine-month change in HAZ as an outcome was used to test the effects of disease severity on HAZ.

Results

A total of 3,~~738~~915 acute episodes were available for analysis. Of these, 2,~~461~~462 were used in building the severity score (on the basis of being associated with anthropometry according to the criteria above, and with ~~duplicate~~shorter episodes in the same month discounted) (see **Figure 2**). Sensitivity analysis did not reveal any bias introduced by removing these episodes. Overall, 93.2% of the non-persistent episodes were associated with a lab result, of which 96.6% were collected within two days of the onset of the episode.

The symptoms considered in the analysis are reported in **Table 1**. The number of episodes associated with each symptom is shown in **Figure 3**. ~~-~~Most symptoms (all except anorexia and dysentery), were most common among the youngest children (<=2 years) and decreased in prevalence with age.

Correlations between the reporting of these symptoms during an episode ranged 0.~~018~~02 to 0.~~643~~64. The strongest correlations were between maternal report of blood and lab-reported blood (rho=0.~~643~~64), followed by nausea and vomiting (rho=0.~~642~~64), total depositions and liquid depositions >=4 (rho=0.~~589~~59), maternal report of blood and maternal report of mucus (rho=0.~~586~~59), malaise and

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stomach pain (rho=0.55055), and malaise and anorexia (rho=0.427). All other correlations were less than 0.4. 43). The correlations between the symptoms as categorized in the final severity score are reported below (**Table 2**).

Effects of Specific Symptoms on short-term Weight Gain

Anorexia, fever, malaise, vomiting and the maximum number of stools per 24/hour period, were all associated with poorer weight gain in months associated with diarrhea (p<=0.010). These symptoms were associated with between 9.69 and 21.328.0 grams less weight gain per each day in the episode during which they occurred (**Table 1**).

The number of days in an episode with>=2, >=4, >=6, and >=8 liquid and or/semi-liquid stools were strongly correlated with each other. Of these, the number of days with >=4 liquid stools led to the greatest improvement in model fit and was therefore retained for further analysis. Each day in which >=4 liquid stools were present was associated with 23.35 grams less weight gain **(Table 1**).

Formation of a Severity Score

In total, six factors were found to be predictive of associated with poorer weight gain: anorexia,. With the exception of malaise, vomiting, fever, the maximum number of stools per 24-hour period, and the number of days with 4 or more liquid per 24-hour period. Anorexia and malaise were strongly correlated (rho=0.432), and therefore only anorexia, which had the greater improvement in weight-model fit, was retained in the final severity score. Other symptoms were more weakly correlated when categorized by duration (rho <0.40) (**Table 2**). These these variables were then categorized into 4 levels according to the duration of the symptom (**Table 3**).The), and the severity score was built by summing these five categorical variables **(Table 3, Figure 4** and **Supplemental Table 1)**. In order to make the score more parsimonious, malaise was excluded while anorexia, which was correlated with malaise (rho=0.43), appeared in multivariate models to explain the association between malaise and weight gain, and **Figures 2**was also perceived as less subjective, was retained. Other symptoms were more weakly correlated with each other (rho <0.40) (**Table 2**), and **4)**.the exclusion of any one from the overall score led to a decrease in model fit. A model that included the overall score also fit better than one in which all variables were included individually.

Episodes were categorized empirically based on their distribution within this dataset as mild (score= 0, no additional symptoms present beyond meeting the minimum criteria for diarrhea), moderate (1-6 (35th-95th percentile) and severe (>=7) (>95th percentile). Using this categorization process, episodes of moderate severity were found todid not predict 51.8g less weight gain over one month than episodes of mild severity (reference value(-25.4g, p=0.186), and episodes of high severity were found to predict 135predicted 132.2 g less weight gain (**Table 4**). When change in WHZ was used as outcome, moderate and severe episodes predicted a loss of 0.049008 (p=0.720) and 0.1827171 (p=<0.001) Z-scores over the month of the episode, respectively (**Table 4**).

Effects of Specific Symptoms and Overall Severity on Linear Growth

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Of all the symptoms tested, only dysentery, as defined by laboratory-observed blood in stool, was independently predictive of poorer linear growth (results not shown). Because dysentery was not included in the severity score, it was then added as an independent variable to the model testing the impact of the severity score overall.

Incident episodes of low severity were not associated with poorer linear growth or changes in HAZ, while each episode of moderate severity predicted 0.~~041cm~~035cm less linear growth and 0.~~010~~009 less in HAZ. Episodes of the highest severity were also unassociated with changes in linear growth and HAZ over the 9 month period (**Table 5**).

Discussion

During diarrheal episodes, anorexia/malaise, fever, vomiting, the number of days with >=4 liquid stools, and the maximum number of depositions per 24/hour period, were the symptoms most strongly associated with poorer weight gain. This suggests the prioritization of these symptoms in the formation of a severity score to characterize mild-to-moderate diarrhea in community-based study settings.

~~Several symptoms of potential interest were not collected and therefore could not be included in our analysis. Temperature, and the maximum number of instances of vomiting in a 24-hour period were not collected, which limits our ability to compare our severity score to that of the 20-point Ruuska and Vesikari score(11), and or the 24-point instrument proposed by Clark (9). Additionally, rectal temperature and dehydration were not noted, so a comparison of the index proposed by Ericsson and subsequently adapted by Jacobs et al could not be applied (25–27).These symptoms require the observation of the child by a trained health worker daily, i.e. a visit to the child at the moment of illness in addition to a caregiver's report. Our final severity score, which is based exclusively on information extracted from the verbal report of a caregiver during twice weekly visits, may have greater utility in a variety of community based study designs where daily clinical assessments are not realistic. However, an ability to compare our severity score to those based on episodes observed in a clinical setting would be of methodological value(28).~~

Several symptoms of potential interest were not collected and therefore could not be included in our analysis, limiting our ability to compare our severity score to that of the 20-point Ruuska and Vesikari score (11), the 24-point instrument proposed by Clark (9), or the index proposed by Ericsson and subsequently adapted by Jacobs et al (25–27). The symptoms that were not collected are those which require measurement or assessment of the child by a trained health worker, i.e. rectal temperature and dehydration. Additionally, the maximum number of emeses in a 24-hour period was not noted. Our final severity score, which is based exclusively on information extracted from the verbal report of a caregiver during three-times weekly visits, is similar to the Vesakari and Clark scores, with the addition of anorexia and the number of days with four or more liquid stools, and minus those components that depend on trained observation, on the level of healthcare received (outpatient, hospitalization, etc.), or on treatment decisions made by a health care professional during the episode (e.g. intravenous rehydration therapy required yes/no) (Supplemental Table 1).

For these reasons, our score may have greater utility than existing severity indices in a variety of community-based study designs where daily clinical assessments are not realistic. However, an ability to compare our score to observations made in a clinical setting would be of methodological value (28), particularly as symptoms based on maternal report are relatively subjective (although more severe symptoms do tend to be more reliably reported (29)). A severity score that includes clinical observations but could also be harmonized with a simplified version based on caregiver reported symptoms, and/or objective measures that can be used in a community-based setting, is also desirable. The association between severity and the risk of hospitalization should also be considered and assessed in a variety of settings (30,31), but because hospitalization and treatment are dependent upon access and not purely clinical need, these are better considered as outcomes that may be associated with diarrheal severity rather than components of diarrheal severity in and of themselves.

Another weakness of our study was a relatively large number of "mild" episodes with a severity score of 0 ~~or 1~~, and the relatively small number of "severe" episodes with a severity score ~~>8~~of 7 or above. ~~-~~ Many episodes were of one or two days in duration, associated with a low (3 or 4) number of maximum stools per 24 hour period, and ~~unassociated with any other symptom, and were therefore, difficult to differentiate between.~~, although they met epidemiological criteria for diarrhea, no others symptoms that might suggest systemic involvement were present. In contrast, episodes required the presence of at least three symptoms to be scored as 'severe' (defined here as approximately the 95th percentile). These observations are consistent with the best available estimates of the proportion of categorization in mild, moderate, and severe episodes in the community setting ~~(7).~~

(7). In ~~contrast, in~~ the "~~high severity~~severe" category, there was a trend towards episodes of higher scores being associated with greater weight loss, i.e. an episode of severity score 15 had a greater impact than one of severity 8 (result not shown). However, because the number of episodes of greater severity was small, they were grouped in a single category. The estimated association between severe episodes and weight gain and linear growth is also correspondingly less precise. While other categorizations of each symptom within the overall score were considered, including categorizations that resulted in a greater proportion of episodes having higher scores, these were less strongly associated with weight gain than the one we present here.

In this index, we assess duration of symptoms differently than previous scores. Both the Vesikari and Clark indexes include the possibility of less than three maximum number of stools/day, which conflicts with the widely accepted definition of diarrhea in a community-based setting as requiring a minimum of three liquid or semi-liquid stools (**Supplemental Table 2**). We defined the bounds of an episode according to the standard epidemiological definition, and then calculated the duration of each symptom under that assumption. Instead of episode duration being included as a separate ~~variable~~component, it was ~~evaluated for inclusion for~~only included indirectly, through the duration of days in which each symptom was present. We believe this is important in evaluating enteric disease caused by a range of both invasive and non-invasive pathogens where the illness syndrome is diverse. In contrast, previous severity scores have been built around the ability of a symptom to discriminate between pathogens: for instance, rotavirus diarrhea is typically associated with significant vomiting and frequent stools, but relatively less fever, and the Vesakari index gives purging frequency and duration a high weight

accordingly[1]. Unfortunately, although common bacterial enteropathogens (ETEC, *Shigella*, and *Campylobacter)* were screened for in this study (21,32), rotavirus was not, and so, while validation of this scoring system against the Vesikari score would be of particular interest, we are unable to do so in this study.

~~Dysentery, as defined by caregiver-reported or laboratory-technician-reported visible blood, was not found to be a predictor of immediate episode-associated weight loss. However, it was independently predictive of poorer linear growth, a finding in agreement with other reports (29). The prevention of dysenteric diarrhea, which is associated with progression to persistent diarrheal (23) and mortality (30) merits prioritization. The importance of dysentery as a cause of linear growth faltering but not acute weight loss suggests that multiple measurement tools for diarrheal severity may be useful. In addition to acute weight loss and linear growth, factors such the likelihood of further infectious disease, the risk of acute dehydration (8), and the risk of mortality, are important child health outcomes that should be considered in score-building (**Figure 1**). The association between severity and the risk of hospitalization should also be considered (31), although measures such as hospitalization, which are dependent upon access and availability and not purely clinical need, vary according to local context and will need to be assessed in a variety of settings (32).~~

We also included in our score the total number of days with four or more liquid stools. The number of total liquid + semi-liquid stools, and the number of days with >=4 liquid+semi-liquid stools were strongly correlated with the maximum number of stools/24 hour period, while the number of days with >=4 liquid stools was relatively less correlated with the total or maximum number of stools and was strongly associated with poorer weight gain even after adjusting for total stools.

Dysentery, as defined by caregiver-reported or laboratory technician reported visible blood, was not found to be a predictor of immediate episode-associated weight loss. However, it was independently predictive of poorer linear growth, a finding in agreement with other reports (33). The prevention of dysenteric diarrhea, which is associated with progression to persistent diarrheal (23) and mortality (34) and merits prioritization. The importance of dysentery as a cause of linear growth faltering but not acute weight loss also suggests that multiple measurement tools for diarrheal severity may be useful. In addition to acute weight loss and linear growth, which we used here, factors such the likelihood of further infectious disease, the risk of acute dehydration (8), and the risk of mortality are important child health outcomes that should be considered in score-building (**Figure 1**).

Standardized and carefully considered measures of diarrheal severity are desirable in clinical trials, intervention studies and descriptive community-based studies of diarrhea in the ~~developing world (33),~~low-income settings (35), and would improve understanding of the impact of disease control measures on morbidity burden. The severity score we derived here is composed of simple components and allows for the meaningful classification of a diarrheal disease episode based upon the most common adverse events associated with diarrhea; depressed weight gain and poorer linear growth, an

[1] With a maximum of 6 points related to vomiting and a maximum of 3 related to fever.

improvement over earlier scores built empirically around symptom frequency. The collection of the input data for this score is highly feasible and are likely available in many extant datasets; further validation could improve the estimates of diarrhea severity and disease burden across epidemiologic settings.

Contributors

MK conceived and designed the study. MK, MPO, PPY designed the data collection tools, monitored recruitment and data collection for the study, and supervised the study. PPY managed and cleaned the data. GL designed and implemented the analysis, CFW, LEC, REB, and DAS provided guidance during the analysis, and contributed to the interpretation of data. All authors helped write and critically review the article, and all authors have approved the final version to be published and agree to be accountable for all aspects of the work. MK and GL are the guarantors.

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Ethical Approval

This study was approved by the Institutional Review boards of the Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (IRB H.22.01.01.02.A), the US Naval Medical Research Center, Silver Springs, MD (IRB NMRCD.2002.0009), and Asociación Benéfica PRISMA, Lima, Peru (no IRB number). All participating families gave signed, informed consent before taking part in the study.

Competing Interests

We have read and understood the BMJ policy on declaration of interests and declare the following interests: None. All authors have completed the ICMJE uniform disclosure form at www.icjme.org/coi_disclosure.pdf (available on request from the corresponding author).

Declaration of Transparency

Gwenyth Lee confirms that this article is an honest, accurate and transparent account of the study reported, that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Data sharing

Raw data used in the analysis is available on request from the corresponding author at mkosek@jhsph.edu. Statistical code is also available upon request.

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Tables and Figures

Table 1: Association of Symptoms with Weight Gain

Caption: In the below model, age (as fractional polynomials, term1= $age^{-2} - 1.16$ and term2= $\ln(age) * age^{-2} - 0.08$), season (with sine/cosine terms), and an AR(1) covariance structure.

	Present in episode yes/no change in weight (g) associated with symptom presence	duration change in weight (g) per days present
Anorexia	-49.1 (-8.8, -9.946.6 (-87.7, -5.6) (p=0.014026)	-12.4 (-22.49 (-23.1, -2.47) (p=0.015013)
Blood in Stool (observed by Mother)	-2.1.8 (-61.47, 57.85) (p=0.952946)	-4.1.3 (-26.2,23.7 (-30.1,21.9) (p=0.920757)
Blood in Stool (observed by lab tech)	-10.63 (-72.58, 93.65) (p=0.803807)	N/A
Fever	-4647.9 (-8889.1, -6.5.7) (p=0.026023)	-17.4 (-33.4, -119.5 (-36.7, -2.3) (p=0.034026)
Nausea	-1.25 (-60.5, 58.28, 57.9) (p=0.970962)	-2.2 (-28.3, 23.829.6, 25.2) (p=0.866875)
Malaise	-49.4 (-84.95 (-85.0, -14.01) (p=0.006)	-9.5 (-17.8, -1.29 (-18.3, -0.4) (p=0.025022)
Mucus in Stool (observed by Mother)	-4.75 (-47.43, 38.03) (p=0.829837)	-0.1 (-14.4, 14.515.0, 15.0) (p=0.994998)
Mucus in Stool (observed by Lab tech)	0.32.9 (-34.4, 41.08, 40.6) (p=0.863879)	N/A
Stomach Pain	-13.9 (-48.89, 21.10) (p=0.427435)	-5.48 (-13.37, 2.52) (p=0.179156)
Vomiting	-56.957.0 (-109.23, -4.7) (p=0.033)	-23.2 (-4628.0, -0.5 (-52.9, 30.8) (p=0.046028)
Four or more liquid stools in a 24/hr period	-44.0 (-8043.1 (-79.6, -7.56.6) (p=0.018021)	-23.65 (-37.65, -9.65) (p=0.001)
Maximum number of stools /24 hr period (continuous)	-9.9 (-18.0, -1.8) (p=0.016)	N/A
Episode Duration (per day - continuous)	-5.1 (-12.5, 2.4) (p=0.181)	N/A

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Table 2: Correlations between symptoms retained in final severity score (N=3,~~738~~915)

Symptoms are categorized here according to the manner that they are included in the final score (0 days with symptom = 0, 1-2 days with symptom=1, 3-4 days with symptom=2, 5+ days with symptom=3).

	Anorexia	Fever	Vomiting	Liquid Stools	Max Stools
Days with Anorexia	1				
Days with Fever	0.~~27~~24	1			
Days with Vomiting	0.~~24~~23	0.~~24~~30	1		
Days with >=4 Liquid Stools	0.~~32~~24	0.~~25~~27	0.~~16~~29	1	
Maximum stools/24hr period	0.~~25~~32	0.~~27~~29	0.~~27~~30	0.~~34~~38	1

Table 3: Severity Scorecard

Symptom	Category	Points
Diarrhea	>=3 liquid or semi-liquid stools per day, for 1-13 days, with gaps of no more than ~~one day~~two days	
Fever	No Fever	+0
	Fever for 1-2 days	+1
	Fever for 3-4 days	+2
	Fever for 5+ days	+3
Anorexia	No Anorexia	+0
	Anorexia for 1-2 days	+1
	Anorexia for 3-4 days	+2
	Anorexia for 5+ days	+3
Vomiting	No Vomiting	+0
	Vomiting for 1-2 days	+1
	Vomiting for 3-4 days	+2
	Vomiting for 5+ days	+3
Liquid Stools	No days with >=4 liquid stools	+0
	1-2 days with >=4 liquid stools	+1
	3-4 days with >=4 liquid stools	+2
	5+ days with >=4 liquid stools	+3
Maximum number of stools in a 24 hour period during the episode	3	+0
	4-5	+1
	6-7	+2
	>=8	+3
TOTAL		0-15

Table 4: Association between Severity Score and change in Weight and Weight-for-Height

The association between incident episodes of diarrheal classified as low (score 0~~-1~~), medium severity (score ~~2-7~~1-6) and high severity (score >=~~8~~7) on the change in weight and weight-for-height Z over 1-month intervals, is shown below. Age (same fractional polynomials as in symptom-specific models) and season (sine and cosine terms) were also adjusted for (beta coefficients not shown).

	1-month change in Weight (g)	1month change in WHZ (Z-score)
Low Severity	ref	ref
Medium Severity	~~-49.3 (-84.8, -13.8~~25.4 (-63.0, 12.2) (p=0.~~007~~186)	~~-0.049 (-0.090, -~~0.008 (-0.052, 0.036) (p=0.~~020~~720)
High Severity	~~-133.0 (-223~~132.2~~, -42.8~~ (-213.6, -50.7) (p=0.~~004~~001)	-0.~~180 (-285.2, -75.7~~171 (-0.266, -0.077) (p=~~<~~0.001)

Table 5: Association between Severity Score and Linear Growth

The association between incident episodes of diarrheal classified as low (score 0~~-1~~), medium severity (score ~~2-7~~1-6) and high severity (score >=~~8~~7) on the change in height and HAZ over 9-month intervals, is shown below. Age (fractional polynomials used to adjust for age in the height model are term1= $age^{-2} - 0.56$ and term3= $\ln(age) * age^{3} - 2.41$), season (sine and cosine terms), stunting, and WHZ (categorized as >0, 0 to -1, and <-1) were also adjusted for (beta coefficients not shown). In the HAZ model, ~~-~~fractional polynomials for age are $age^{-2} - 1.80$ and ~~=~~ $\ln(age) * age^{2} - 0.53$.

	9mo change in Ht (cm)	9mo change in HAZ (Z-score)
Low-severity episodes (incidence)	-0.~~02~~1014 (-0.~~04~~3042, 0.~~00~~1015) (p=0.~~05~~7348)	-0.~~00~~4001 (-0.~~1~~11012, 0.~~00~~3009) (p=0.~~29~~9755)
Medium-severity episodes	-0.~~04~~1035 (-0.~~06~~5056, -0.~~01~~6014) (p=0.001)	-0.~~01~~0009 (-0.~~1~~19016, -0.001) (p=0.~~02~~2025)
High-severity episodes	-0.~~00~~3011 (-0.~~06~~9067, 0.~~07~~4044) (p=0.~~93~~6690)	-0.~~01~~1008 (-0.~~03~~6,028, 0.~~01~~5012) (p-=0.~~42~~3439)
Episodes of dysentery	-0.~~11~~3112 (-0.189, -0.~~03~~8036) (p=0.~~00~~3004)	-0.~~03~~4033 (-0.~~06~~2061, -0.~~00~~7006) (p=0.~~01~~3018)

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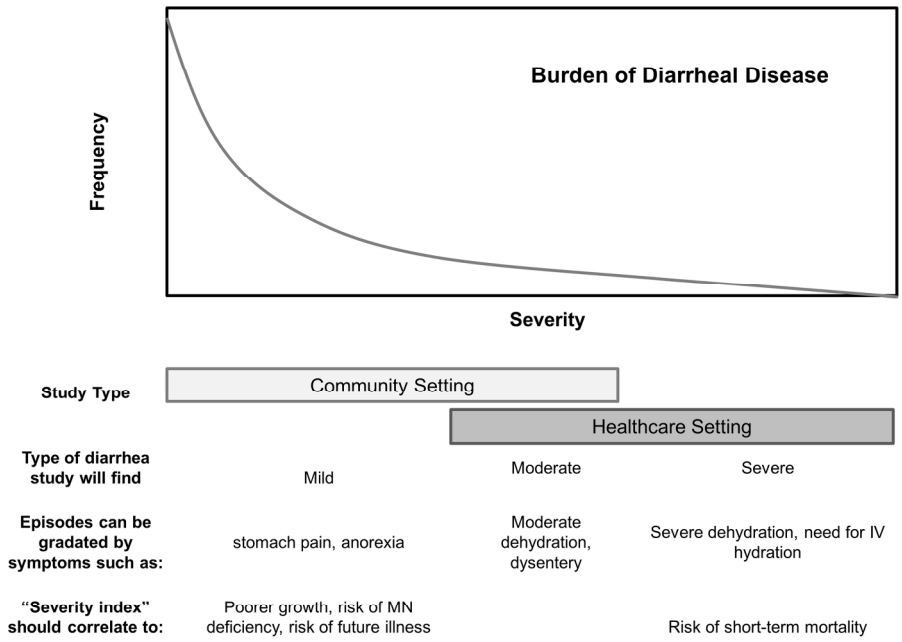
Figure 1: Conceptual Diagram of Idealized Severity Score

~~**Figure 2: Example of Severity Score Applied to an Episode:** A 6-day episode with fever on 3 days (+2), anorexia on 0 days (+0), vomiting on 1 day (+1), a maximum total number of stools/day of 6 (+2) and a total of 3 days with 4 or more liquid stools (+2) = total severity score of 7.~~

Figure 2: Episodes included in the analysis

Figure 3: Distribution of Symptoms: Out of all episodes (n=3,~~738~~915)

Figure 4: Histogram of severity score distribution: The y-axis (frequency) indicates the number of episodes assigned to the score (N= 3,~~738~~915).



Conceptual Diagram of Idealized Severity Score
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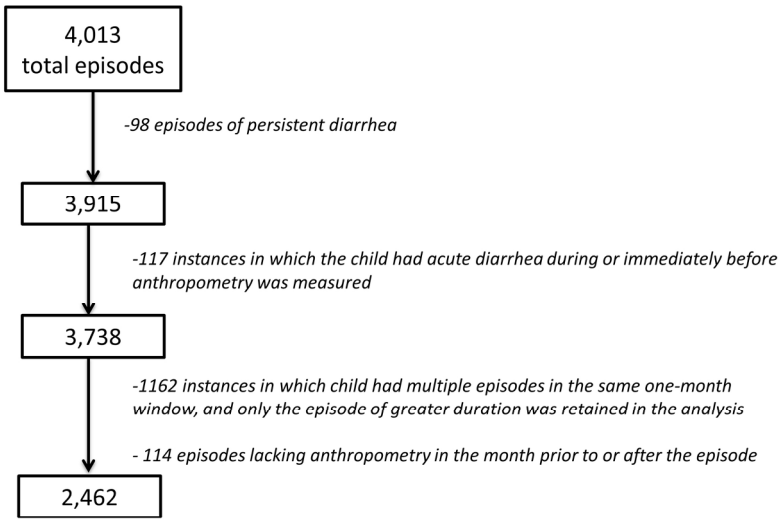

Episodes included in the analysis
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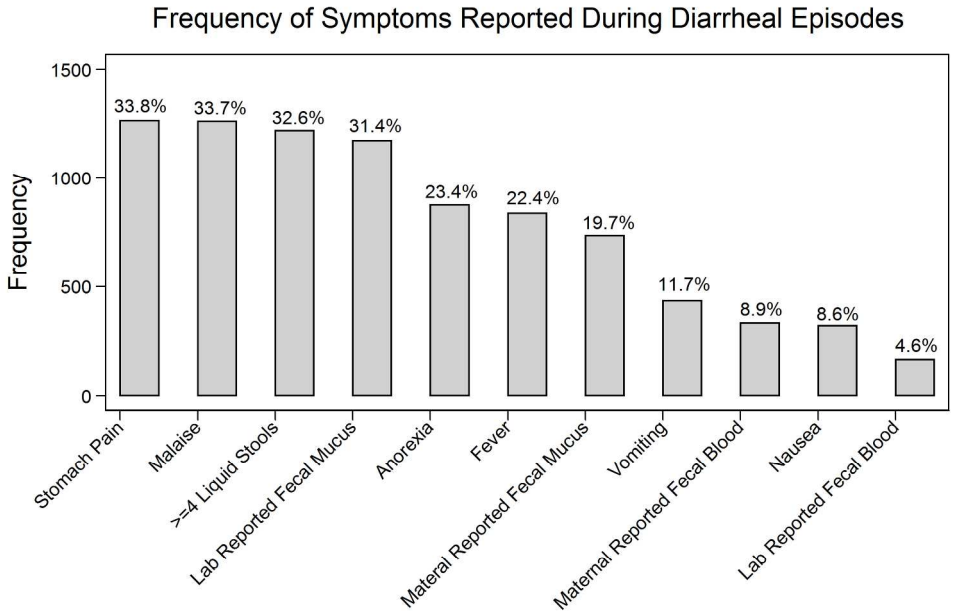

Distribution of Symptoms: Out of all episodes (n=3,915)
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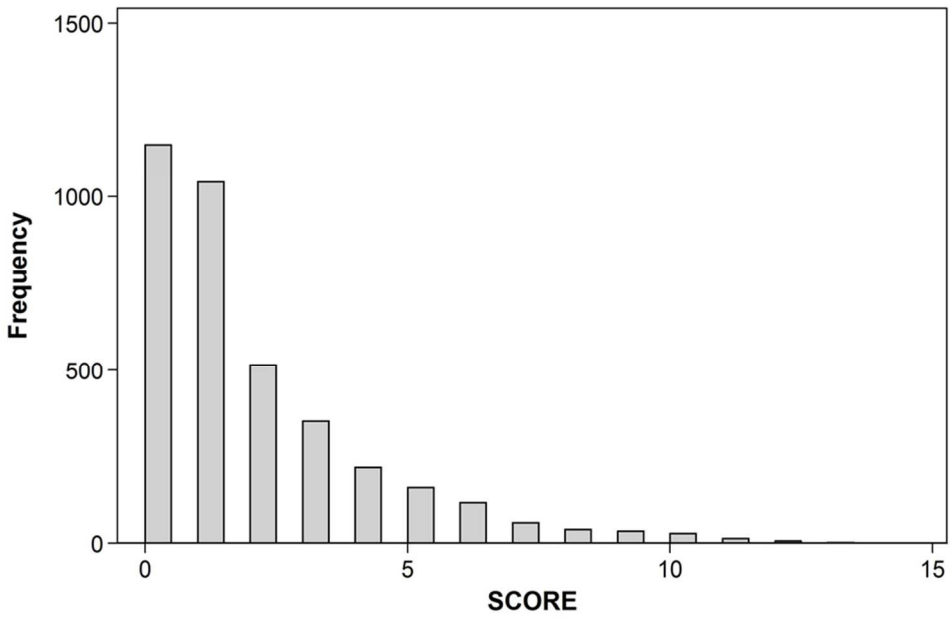

Figure 4: Histogram of severity score distribution: The y-axis (frequency) indicates the number of episodes assigned to the score (N= 3,915).
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Supplemental Table 1: Severity score calculation applied to several examples:

	Sun	Mon	Tues	Wed	Thurs	Fri	Sat
Fever	no	YES	YES	YES	no	no	no
Anorexia	no	no	no	no	no	no	no
Vomiting	no	no	YES	no	no	no	no
Total Number of solid stools	0	0	0	1	0	0	0
Total Number of semi-liquid stools	3	4	4	5	6	3	2
Total number of Liquid stools	0	0	4	4	4	0	0
Total stools	3	4	8	10	10	3	2

(i) A 6-day episode with fever on 3 days (+2), anorexia on 0 days (+0), vomiting on 1 day (+1), a maximum total number of stools/day of 10 (+3) and a total of 3 days with 4 or more liquid stools (+2) = total severity score of 8.

	Sun	Mon	Tues	Wed	Thurs	Fri	Sat
Fever	no	no	no	no	no	no	no
Anorexia	no	no	YES	no	no	no	no
Vomiting	no	no	no	no	no	no	no
Total Number of solid stools	2	2	0	0	1	2	1
Total Number of semi-liquid stools	0	2	2	1	0	0	0
Total number of Liquid stools	0	0	1	2	0	0	0
Total stools	2	4	3	3	1	2	1

(i) A 2-day episode with no fever (+0), anorexia on 1 days (+0), no vomiting (+0), a maximum total number of stools/day of 3 (+0) and no days with 4 or more liquid stools (+0) = total severity score of 1.

	Sun	Mon	Tues	Wed	Thurs	Fri	Sat
Fever	no	no	no	no	no	no	no
Anorexia	no	no	no	no	no	no	no
Vomiting	no	no	no	no	YES	YES	no
Total Number of solid stools	3	2	1	0	0	1	0
Total Number of semi-liquid stools	0	0	3	3	2	3	0
Total number of Liquid stools	0	0	0	0	0	0	0
Total stools	3	2	4	3	2	4	0

(ii) A 4-day episode (Tues-Fri) with no fever (+0), no anorexia (+0), two days of vomiting (+1), a maximum total number of stools/day of 4 (+1) and no days with 4 or more liquid stools (+0) = total severity score of 2.

Supplemental Table 2: Comparison of Severity Scores

Direct Observation (DO) or caregiver Report (CR)	Score component	Vesakari (11)	Clark (9)	Modified Vesikari (13)	Our Score	Scoring
Non-specific						
CR	**Duration of Diarrhea**	1-4 days	1-4 days	1-4 days	-	1
		5 days	2-7 days	5 days	-	2
		>=6 days	>=8 days	>=6 days	-	3
CR	**Max number of stools /day**	1-3	2-4	1-3	4-5	1
		4-5	5-7	4-5	6-7	2
		>=6	>=8	>=6	>=8	3
CR	**Duration of >=4 Liquid Stools (days)**	-	-	-	1-2 days	1
		-	-	-	3-4 days	2
		-	-	-	>=5 days	3
Vomiting						
CR	**Duration of vomiting (days)**	1 day	1-2 days	1 day	1-2 days	1
		2 days	3-5 days	2 days	3-4 days	2
		>=3 days	>=6 days	>=3 days	>=5 days	3
CR	**Number of emeses/day**	1	1-3	1	-	1
		2-4	4-6	2-4	-	2
		>=5	>=7	>=5	-	3
Fever						
CR	**Duration of fever (days)**	-	1-2 days	-	1-2 days	1
		-	3-4 days	-	3-4 days	2
		-	>=5 days	-	>=5 days	3
DO	**Temperature / Rectal Temperature**	37.1-38.4°C	38.1-38.2°C	37.1 – 38.4°C	-	1
		38.5-38.9°C	38.3-38.7°C	38.5 – 38.9°C	-	2
		>= 39.0°C	38.8°C	>=39.0°C	-	3
Dehydration / Liquid Stools						
DO	**Dehydration**	-	-	-	-	1
		1-5%	-	-	-	2
		>=6%	-	-	-	3
Behavioral Signs						
CR	**Behavioral signs**	-	irritable/less playful	-	-	1
		-	lethargic/listless	-	-	2
		-	seizure	-	-	3
CR	**Behavioral signs (duration)**	-	1-2 days	-	-	1
		-	3-4 days	-	-	2
		-	>=5 days	-	-	3
CR	**Anorexia**	-	-	-	1-2 days	1
		-	-	-	3-4 days	2
		-	-	-	>=5 days	3
Treatment						
	Treatment	Rehydration	-	Rehydration	-	1
		Hospitalization		Hospitalization	-	2
	Health care provider visits		-	Outpatient	-	2
				E.D.	-	3
	Total	**20 points**	**24 points**		**15**	