Effects of Cryptosporidium parvum Infection in Peruvian Children: Growth Faltering and Subsequent Catch-up Growth

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The authors conducted a 2-year (1989–1991) community-based longitudinal study in a shantytown in Lima, Peru, to examine the effect of Cryptosporidium parvum infection on child growth during the year following the onset of infection. A cohort of children, aged 0–3 months at recruitment, was followed monthly for anthropometrics, weekly for stool samples, and daily for diarrheal status. Data from 185 children in the cohort permitted a comparison of growth in C. parvum–infected and noninfected children. The analyses fitted smooth, flexible curves with a linear random-effects model to estimate growth differences between C. parvum–infected and noninfected children. Children infected with C. parvum experienced growth faltering, both in weight and in height, for several months after the onset of infection, followed by a period of catch-up growth. Younger children took longer to catch up in weight than did older children. Catch-up growth, however, did not occur in children infected between ages 0 and 5 months. These children did not catch up in height, and one year after infection they exhibited an average deficit of 0.95 cm (95% confidence interval (CI) 0.38–1.53) relative to noninfected children of similar age. Stunted children who became infected also did not catch up in either weight or height, and one year after infection they exhibited a height deficit of 1.05 cm (95% CI 0.46–1.66) relative to noninfected, stunted children of similar age. These results indicate that Cryptosporidium parvum has a lasting adverse effect on linear (height) growth, especially when acquired during infancy and when children are stunted before they become infected. Am J Epidemiol 1998; 148:497–506.

Cryptosporidium parvum; diarrhea, infantile; growth disorders; infection; longitudinal studies; nutrition disorders; smoothing splines; statistics

Cryptosporidium parvum is an important cause of diarrhea worldwide (1, 2). In communities where C. parvum is endemic and hygiene practices or water quality are poor, infection occurs early in life (1–4). Previous epidemiologic studies (5–8) have demonstrated an association between C. parvum infection and malnutrition, but these studies have not determined the direction of this association. To examine the effect of cryptosporidiosis on child growth, we conducted a 2-year community-based longitudinal study of Peruvian children aged 0–3 months at recruitment. This investigation seeks to examine the effects of C. parvum infection on weight gain and linear (height) growth in children less than 2 years of age during the year following the onset of first infection with C. parvum. In an earlier analysis (9), we found that C. parvum infection causes slower weight gain during the first month of infection, while malnutrition did not appear to be a significant risk factor for C. parvum infection.

To model the effect of C. parvum infection on growth, we use regression splines (10, 11) to estimate growth differences between C. parvum–infected and noninfected children. The advantage of regression splines over other parametric regression models is that they can be used to estimate smooth curves of unknown shape. Although regression spline smoothing is not a new technique, it has not been widely used in epidemiologic studies. In this investigation, we describe the use of regression splines for longitudinal data analysis to study periods of slower growth and subsequent recovery (i.e., catch-up) following the onset of C. parvum infection.
MATERIALS AND METHODS

The study was conducted in Pampas de San Juan de Miraflores, a peri-urban shantytown (pueblo joven) in Lima, Peru, with approximately 35,000 residents, of whom 25 percent are children under age 5 years. Most households in this community belong to the same socioeconomic stratum. The majority of houses are temporary structures made of woven thatch and supported by wooden poles, and a small number are made of brick. Fewer than one-half of the houses have latrines or sewage connections. Municipal trucks supply most households with water, which is then stored in cisterns or barrels that often become contaminated with fecal matter (12). Previous studies (4, 9, 13) report more detailed information on the community. This study was approved by the Committee of Human Research of the Johns Hopkins School of Hygiene and Public Health and by the Ethics Committee of A. B. PRISMA.

Women in their final trimester of pregnancy were randomly selected from the censused community and asked to participate in the study. Census information was obtained from A. B. PRISMA, a local non-governmental organization working in this community. Participant women were asked about their household weekly expenses and source of water. From September to December 1989, 80 infants aged 0–3 months were recruited. Between January 1990 and June 1991, approximately ten newborns were recruited each month.

Children enrolled in the study were followed from September 1989 to November 1991. Each month, field workers visited the participant households. The field workers measured the enrolled children’s weight with Salter scales (Salter Housewares Ltd., Tonbridge, Kent, England). They measured the children’s length with a locally constructed wooden length platform with a sliding footboard. Field workers also collected weekly stool specimens, which were examined for *C. parvum* as previously described (9, 14). Bacterial and viral enteropathogens were not determined. Stool specimens were classified as *C. parvum*-positive if at least one oocyst of *C. parvum* was detected in the sample. Twice a week, field workers retrospectively assessed the children’s daily diarrheal status by questioning mothers or caretakers about the number of liquid or semi-liquid stools the child had passed on the day of the interview and in the preceding 3 days. We defined a day of diarrhea as one in which a child passed ≥3 liquid or semi-liquid stools; a diarrheal episode as ≥1 days of diarrhea followed by ≥2 diarrhea-free days; and a persistent episode as ≥14 days of diarrhea (15).

For a given child, we defined a “study interval” as the interval between two consecutive anthropometric measurements, and the first study interval as the 30-day period prior to the first anthropometric measurement. Therefore, each child contributed to the analysis several study intervals of variable length. We excluded from the analysis study intervals >60 days or with <12 days of diarrheal surveillance or <2 stool examinations for *C. parvum* per 30 child-days. We also excluded from the analysis children infected with *C. parvum* prior to their first anthropometric measurement, children with <4 anthropometric measurements, and post-*C. parvum* infection study intervals of children who had <4 anthropometric measurements after the onset of the first *C. parvum* infection. The mean length of the study intervals was 31 days (standard deviation 7 days).

Next, we turn to the definition of the onset of infection. Anthropometric measurements and stool specimens were rarely collected at the same time. Therefore, for analytical convenience, we defined the onset of *C. parvum* infection of a child in relation to the dates on which the most recent anthropometric measurements were taken. A child was considered free of infection up to the anthropometric measurement preceding the first *C. parvum*-positive stool sample, and the date of this measurement was labeled the zero-time of the onset of *C. parvum* infection.

Study sample

A total of 253 mothers were invited to enter the study. Thirty mothers declined; one child died of pneumonia early in the study; 22 children’s families emigrated from the community within 2 months of admission to the study; six children had a *C. parvum*-positive stool prior to their first study interval; and 26 children were excluded either because none of their study intervals met criteria for analysis or because they had fewer than four anthropometric measurements. Thus, data were available for 77 percent (185/239) of children enrolled in the study. A total of 8,594 weekly stool specimens and 59,497 assessments of daily diarrheal status were collected in the 2,050 study intervals that met the criteria for analysis.

Eighty-eight (88/185 or 48 percent) of the children aged 0–23 months included in the analysis became infected with *C. parvum* during the study. Of these 88 children, 69 (69/88 or 78 percent) had at least four anthropometric measurements after the onset of infection study intervals of children aged 0–23 months included in the analysis became infected with *C. parvum* during the study. Of these 88 children, 69 (69/88 or 78 percent) had at least four anthropometric measurements after the onset of infection. Of the 69 children, 63 were infected between 0 and 17 months of age (the age strata considered in our analysis). No significant differences were observed between infected children whose post-infection study intervals met criteria for analysis and those whose intervals did not meet the criteria, when compared by total weekly expenses (*p* = 0.73), weekly food ex-

penses \( p = 0.82 \), number of diarrheal episodes \( p = 0.87 \), number of persistent diarrheal episodes \( p = 0.14 \), sex \( p = 0.18 \), or water source \( p = 0.21 \). No significant differences were observed between \( C. parvum \)-infected and noninfected children when compared by total weekly expenses \( p = 0.73 \), weekly food expenses \( p = 0.82 \), or water quality \( p = 0.77 \). No significant differences were observed among \( C. parvum \)-infected children of different age strata when compared by total weekly expenses \( p = 0.94 \), weekly food expenses \( p = 0.97 \), or water quality \( p = 0.67 \).

**Biostatistical methods**

To model differences in temporal growth patterns between \( C. parvum \)-infected and noninfected children, we fitted smooth functions known as regression splines (16, 17) with a linear random-effects model (18). Our growth model has two advantages over other parametric models of growth. First, it permits one to fit a growth curve for each child. These individual growth curves are distributed around a central curve that represents the expected growth in the population. Second, regression splines fit smooth, flexible curves to the data that permit one to estimate curves of unknown form. For this reason, our growth model is useful to estimate a growth curve which departs from a reference growth curve after the onset of an event such as a \( C. parvum \) infection (see figure 1).

A regression spline fits a smooth curve to a set of \((x, y)\) points (16). This curve consists of piecewise polynomials joined together at a number of prespecified points called “knots.” We use a particular type of regression spline, called the natural cubic B-spline, primarily because it is simple to calculate and because it can be fitted with a linear regression model (16). A regression spline with \( p \) knots, expressed as a linear combination of elements from the natural cubic B-spline basis, uses \( p + 2 \) parameters. However, if the model includes an intercept, only \( p + 1 \) parameters are required (17).

In this investigation, the \( x \)-axis represents the age in months. Depending on the model, the \( y \)-axis represents the weight or height. The analysis estimates two separate curves. One curve estimates the mean growth curve of children not infected with \( C. parvum \), and the other curve estimates the mean difference in growth between \( C. parvum \)-infected and noninfected children after the onset of infection. These curves are referred to as the “normal-growth curve” and the “departure-from-normal-growth curve,” respectively (see figure 1).

With our regression model, we examined the interaction effects between \( C. parvum \) infection and the following variables: age at onset of infection, prior nutritional status, and whether the infection was symptomatic or asymptomatic (characterized by the presence or absence of diarrhea at the time of infection). For age at onset of infection, we stratified children infected with \( C. parvum \) by their age at onset of infection into 6-month age strata: 0–5, 6–11, 12–17,
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and 18–23 months. To study the interaction effects between *C. parvum* infection and age at onset of infection, we fitted departure-from-normal-growth curves for each age stratum using a single regression model. Sufficient data were available to estimate the effect of *C. parvum* infection on growth during the year following the onset of infection for children infected between 0 to 11 months of age. However, in children infected between 12 and 17 months of age, data were only sufficient to estimate growth effects for up to 7 months after infection. We did not have sufficient data to estimate the effect of *C. parvum* infection on growth between 18 and 23 months of age.

To study the interaction effects between *C. parvum* infection and prior nutritional status, we stratified the children’s study intervals as stunted (defined for the purpose of the analysis as one standard deviation below the expected National Center for Health Statistics height-for-age score) or nonstunted. We also stratified children infected with *C. parvum* by whether or not they were stunted in the previous 3 months prior to the onset of infection. To study whether prior stunting increases the effect of *C. parvum* infection on growth, our regression analysis estimated four separate curves: 1) a normal-growth curve for nonstunted, noninfected children, 2) a normal-growth curve for stunted, noninfected children, 3) a departure-from-normal-growth curve for nonstunted, infected children, and 4) a departure-from-normal-growth curve for stunted, infected children. The growth of infected children who were not stunted prior to infection was compared with that of noninfected, nonstunted children. Similarly, the growth of children who became infected with *C. parvum* and who were stunted prior to infection was compared with that of noninfected, stunted children.

Assessment of growth differences Our growth models estimated the difference in weight or height between *C. parvum*-infected and noninfected children during the year following the onset of their *C. parvum* infection. Accordingly, the dependent variable was either weight or height at the end of a study interval. The independent variables were: 1) the B-spline elements that form the normal-growth spline; 2) the B-spline elements that form the stratum-specific departure-from-normal-growth splines; 3) the presence or absence of non-*C. parvum* diarrhea during study intervals prior to the onset of *C. parvum* infection; 4) the presence or absence of non-*C. parvum* diarrhea during study intervals prior to the onset of *C. parvum* infection; 5) the presence or absence of non-*C. parvum* diarrhea during study intervals after the onset of *C. parvum* infection; 6) the presence or absence of stunting in the previous study interval; and, 7) sex. The elements in 2) combine to model the effect of *C. parvum* infection on growth, after controlling for non-*C. parvum* diarrhea, prior nutritional status, and sex. Variable 3 controls for the effect of pre-infection non-*C. parvum* diarrhea on growth. Variable 4 controls for the difference in effect of pre-infection non-*C. parvum* diarrhea on growth between children aged <6 months and ≥6 months. We included variable 4 in the model because we observed that the effect of diarrhea on growth in children aged <6 months was significantly different from that in children aged ≥6 months. Variable 5 controls for the effect of post-infection non-*C. parvum* diarrhea on growth. Variable 6 controls for the effect of prior stunting on growth.

Heterogeneity across children was modeled with a child-specific random intercept (18). To fit the random-effects regression model, we used a linear mixed model algorithm (19) developed for the S-Plus software package (StatSci, Seattle, Washington). We also calculated 95% pointwise confidence intervals for the stratum-specific departure-from-normal-growth curves (17). We did not need to adjust for seasonality because we controlled for its effect on growth by staggering the children’s enrollment into the study.

Regression model

To fit the regression splines for the normal-growth and the departure-from-normal-growth curves, we use the following linear random-effects model:

\[ y_{ij} = \alpha_i + f(t_{ij}; \beta) + I_{ng}(t^*_r; \delta_i) + h(t_{ij}, z_{ij-1}; \gamma) + D(t_{ij}, d_{ij}, T_i; \lambda) + \tau_s + \epsilon_{ij}, \]

where \( i = 1, \ldots, n \), indexes the children in the sample; \( j = 1, \ldots, m_i \), indexes the anthropometric measurements of child \( i \); \( y_{ij} \), \( j = 1, \ldots, m_i \), are the weight or height measurements for child \( i \); \( t_{ij}, j = 1, \ldots, m_i \), are the ages for child \( i \) at which the anthropometric measurements were taken; \( T_i \) is the element in the sequence of times \( t_i \) that represents the zero-time onset of infection (i.e., time origin to measure time after the infection); and, \( t^*_r \) are the times (in months) after the onset of infection, where \( t^* = t - T \) for \( t > T \), and 0 otherwise. The \( \alpha_i \) represent the initial values for weight or height, which vary by children. Analyses use a number of stratifications of the children. The index \( r = 1, \ldots, R \), represents the strata in a particular analysis. The function \( f(t_i; \beta) \) represents...
the normal-growth curve. The function $g_{r}(t^*; \delta_r)$ represents the departure-from-normal-growth curve for the $r$th stratum, $I_{ir} = 1$ if child $i$ was infected for the first time in the $r$th stratum and $I_{ir} = 0$ otherwise. The function $h(t_{ij}, z_{i-1}; \gamma)$ represents the difference in growth between stunted and nonstunted children, and $z_{ij-1} = 0$ otherwise. The function $D(t, d, T; \lambda)$ represents the effect of non-$C.\ parvum$ diarrhea on growth, and $d_{ij} = 1$ if child $i$ had diarrhea between the times $t_{ij-1} - T_i$ and $t_{ij}$, and $d_{ij} = 0$ otherwise. $\beta = (\beta_1, \ldots, \beta_{p+1})$, $\delta_r = (\delta_{r1}, \ldots, \delta_{r,p+1})$, $\gamma = (\gamma_1, \ldots, \gamma_{p+1})$, and $\lambda = (\lambda_1, \lambda_2, \lambda_3)$ are the regression parameters for $f(t; \beta)$, $g_{r}(t^*; \delta_r)$, $h(t; \gamma)$, and $D(t, d; T; \lambda)$, respectively. Expressions for these functions appear below. The term $s_i$ is an indicator of the child’s sex, $s_i = 1$ if female, and 0 if male; $\tau$, the regression parameter for $s_i$, represents the sex effect on growth; and, $e_{ij}$ represents the error term. We assume that conditional on the model’s parameters, the $e_{ij}$ are independent and normally distributed. Further assumptions underlying the error structure are described by Laird and Ware (18).

The functions $f(t; \beta)$ and $g_{r}(t^*; \delta_r)$, may be expressed as

$$f(t; \beta) = \sum_{k=1}^{p+1} \beta_k N_k(t),$$

$$g_{r}(t^*; \delta_r) = \sum_{k=1}^{p+1} \delta_{rk} N_k(t^*),$$

where $p$ is the number of knots for both $f(t; \beta)$ and $g_{r}(t^*; \delta_r)$, and the $N_k$ are the elements of the natural cubic B-spline basis. The natural cubic B-spline elements for $f(t; \beta)$ and $g_{r}(t^*; \delta_r)$ were calculated with a modified version of the ns() function of S-Plus.

When age at the onset of $C.\ parvum$ infection is included in the model, there are three departure-from-normal-growth curves ($R = 3$); when prior nutritional status is included in the model, there are two departure-from-normal-growth curves ($R = 2$); and, when the presence or absence of $C.\ parvum$ diarrhea is included in the model, there are two departure-from-normal-growth curves ($R = 2$).

The growth curve of children not infected with $C.\ parvum$ is $f(t; \beta)$ and the growth of infected children in the $r$th stratum is $f(t; \beta)$ for $t < T_i$, and $f(t; \beta) + g_{r}(t^*; \delta_r)$, for $t \geq T_i$. Because we are interested in inferences about the difference in growth between infected and noninfected children, we calculated 95 percent confidence intervals (CI) for $g_{r}(t^*; \delta_r)$. To calculate pointwise 95 percent CI for the age-stratum specific departure-from-normal-growth curves, we used

$$g_{r}(t^*; \delta_r) \pm 1.96 \sqrt{\hat{V}(\delta_r)N(t)},$$

where $g_{r}(t^*; \delta_r)$ is the estimate of $g_{r}(t^*; \delta_r)$, $\hat{\delta}_r$ is the estimate of $\delta_r$, and $\hat{V}(\delta_r)$ is the estimate of $V(\delta_r)$, the variance-covariance matrix of $\hat{\delta}_r$.

For convenience, the knots were chosen at 1, 3, 6, and 12 months, but this choice is not critical. Indeed, to examine the sensitivity of the results to the choice of the knots, we perturbed their position and found that the parameter estimates changed only slightly.

The values $D(t_{ij}, d_{ij}; T_i; \lambda_{ij})$ control for the confounding effect of non-$C.\ parvum$ diarrhea on growth. These are

$$D(t_{ij}, d_{ij}; T_i; \lambda_{ij}) = d_{ij}\lambda_1[T_i - t_{ij}]_+ + \lambda_2[t_{ij} - 6]_+ \times [T_i - t_{ij}]_+ + \lambda_3[t_{ij} - T_i]_+,$$

where $[t - T]_+ = t - T$ for $t > T$, and 0 otherwise. Thus, for the $i$th child $[T_i - t_{ij}]_+$ indicates whether the time $t_{ij}$ of the $j$th anthropometric measurement is prior to $T_i$; the product $[t_{ij} - 6]_+ \times [T_i - t_{ij}]_+$ indicates whether time $t_{ij}$ of the $j$th anthropometric measurement is prior to $T_i$ for children aged $\geq 6$ months; and $[t_{ij} - T_i]_+$ indicates whether $t_{ij}$ is posterior to the onset of infection.

**RESULTS**

Of the 63 children who became infected with $C.\ parvum$ between 0 and 17 months of age and who met the criteria for analysis, only 3 percent (2/63) presented persistent diarrhea at the time of infection. After infection, infected children gained weight and height more slowly than did noninfected children of similar age, regardless of whether the infection was symptomatic or asymptomatic.
Age at onset of infection

Younger age at infection intensified the effect of *C. parvum* infection on growth (figure 2). Children infected with *C. parvum* between ages 0 and 5 months gained weight significantly more slowly than did noninfected children of similar age for the first 1.6 months. By 1.6 months after infection, these children had an estimated weight deficit of 456 g (95 percent CI 199–713) relative to noninfected children of similar age. Subsequently, these children gained weight more rapidly than did noninfected children of similar age, and catch-up weight was complete at 6.0 months after infection. A similar adverse effect was observed on linear (height) growth. The slower period of linear growth extended from onset to 2.8 months after infection. At 2.8 months after infection, these children had a height deficit of 0.84 cm (95 percent CI 0.29–1.38) relative to noninfected children of similar age. No subsequent height catch-up occurred, and one year after infection these infected children exhibited a height deficit of 0.95 cm (95 percent CI 0.38–1.53) relative to noninfected children of similar age.

Children infected with *C. parvum* between ages 6 and 11 months had a similar slowing of weight and height gain relative to noninfected children of similar age, but of a smaller magnitude. These children recovered their deficits in weight and height. Catch-up in weight was complete at 4.1 months after infection and catch-up in height at 12 months after infection.

Children infected with *C. parvum* between ages 12 and 17 months grew significantly more slowly in weight than did noninfected children of similar age. Catch-up weight was complete at approximately 3.3 months after infection. These children also gained height significantly more slowly than did noninfected children of similar age. By 7 months after infection, children infected with *C. parvum* between ages 12 and 17 months had not caught up and exhibited a height deficit of 0.52 cm (95 percent CI −0.14 to 1.19).

Prior nutritional status

Stunting prior to *C. parvum* infection increased the magnitude and duration of the effect of *C. parvum* infection on growth (figure 3). Children infected with *C. parvum* between ages 0 and 17 months and who were stunted prior to infection (n = 23) tended to show more growth loss than did children with asymptomatic *C. parvum* infection. This difference, however, was not statistically significant for either weight (p = 0.11) or height (p = 0.10) (p values by likelihood ratio test).

DISCUSSION

This study demonstrates that *Cryptosporidium parvum* infection, whether it is symptomatic or asymptomatic, has a long-lasting adverse effect on weight gain and linear (height) growth. In addition, younger age and prior stunting intensified the effect. Indeed, stunted children who became infected with *C. parvum* were 1 cm shorter than were noninfected, stunted children one year after the onset of infection.

A recent independent study in Guinea-Bissau (20) suggested that *C. parvum* infection has lasting adverse effects on growth in weight and height in children under age 2 years. In our study, we found lasting adverse effects on height; a lasting adverse effect on weight was observed only in children who were stunted before they became infected with *C. parvum*. Differences between the Guinea-Bissau study and our study may be explained as follows: 1) children in Guinea-Bissau have higher rates of acute and chronic malnutrition than do Peruvian children who live in Pampas de San Juan de Miraflores; 2) children in Guinea-Bissau with *C. parvum*-associated diarrhea have higher mortality rates than do noninfected children (21); 3) the Guinea-Bissau study only examined children with *C. parvum* diarrhea, while our study included children with symptomatic and asymptomatic infections; and, 4) the analytical model from the Guinea-Bissau study did not control for the potential confounding effect of other causes of diarrhea on...
Growth Effects of *Cryptosporidium parvum* Infection in Children

**FIGURE 2.** Departure-from-normal-growth curves following the onset of *Cryptosporidium parvum* infection, stratified by age at onset of infection. Dotted lines represent the mean difference in weight or height growth between infected and noninfected children. The shaded regions represent 95 percent pointwise confidence intervals. The zero-level horizontal represents the null hypothesis that no growth difference exists between *C. parvum*-infected and noninfected children. A negative slope represents growth retardation and a positive slope represents catch-up growth. Panels in the left column represent deviations from normal weight growth and panels in the right column represent deviations from normal height growth. The upper, middle, and lower rows represent the differences in growth for children infected with *C. parvum* at ages 0–5, 6–11, and 12–17 months, respectively. When the upper extreme of a 95 percent pointwise confidence interval is below the zero-level horizontal, the difference in growth between infected and noninfected children is statistically significant at the 0.05 level. Differences in effect by age at onset of infection were not statistically significant for weight (p = 0.71), but were statistically significant for height (p < 0.001) (p values by likelihood ratio test).
FIGURE 3. Departure-from-normal-growth curves following the onset of Cryptosporidium parvum infection, stratified by whether or not children were stunted prior to infection (defined as a height-for-age Z score less than -1). Dotted lines represent the mean difference in weight or height growth between infected and noninfected children. The shaded regions represent 95 percent pointwise confidence intervals. Panels in the left column represent deviations from normal weight gain and panels in the right column represent deviations from normal linear growth. The upper and lower rows represent the differences in growth for children infected with C. parvum with and without prior stunting, respectively. For the upper row, the zero-level horizontal represents the null hypothesis that no growth difference exists between C. parvum-infected and noninfected children who were stunted. For the lower row, the zero-level horizontal represents the null hypothesis that no growth difference exists between C. parvum-infected and noninfected children who were not stunted. A negative slope represents growth retardation and a positive slope represents catch-up growth. When the upper extreme of a 95 percent pointwise confidence interval is below the zero-level horizontal, the difference in growth between infected and noninfected children is statistically significant at the 0.05 level. Differences in effect by stunting prior to infection were statistically significant for weight ($p = 0.04$) and for height ($p < 0.001$) ($p$ values by likelihood ratio test).

growth and did not examine the interaction of the effect of C. parvum on growth with other variables, whereas our study did both. Despite these differences, both studies support the hypothesis that cryptosporidiosis has an adverse effect on growth, especially when infection is acquired during infancy.

We used smooth, flexible functions with a linear random-effects model for the longitudinal analysis of growth. Until recently, however, smoothing was used only as a tool for exploratory data analysis (16). The advantages of our growth model over other models are that it 1) allows one to use longitudinal data collected at irregular time intervals; 2) incorporates the heterogeneity in the growth patterns of children; and, 3) furnishes a smooth, flexible curve that fits the data better than do other parametric models because it does not require a rigid functional form to represent the effect of C. parvum infection on growth. With these advantages, our growth model provides an accurate representation of the longitudinal course of growth after the onset of C. parvum infection.

The process of catch-up growth has been described in cases of children recovering from shigellosis (22) and celiac disease (23). Although catch-up growth is a well-known phenomenon, both in animals (24) and in humans (25), its mechanism remains poorly understood (26–28). Catch-up growth may occur for any of the following reasons: 1) increased appetite and thus
increased intake; 2) increased absorption; or, 3) more efficient utilization of calories. In a study of eight Jamaican children recovering from protein-calorie malnutrition (29), growth rates were 15 times more rapid than those of normal children of similar age, and five times higher than those of normal children of similar height and weight. For these children, periods of rapid growth were associated with high food intake. Previous studies in the Pampas community and studies in other countries have demonstrated that, following nutritional rehabilitation, severely malnourished children catch up in weight but not in height (13, 29). Catch-up in height is possible, although the process appears to be slower than catch-up in weight (30). In our study, infected children who caught up in weight did not necessarily catch up in height by one year after infection onset. When catch-up in height did occur, it took longer than did catch-up in weight. On average, children who caught up in height had also caught up in weight.

We did not have sufficient data to compute simultaneously stratified effects of \textit{C. parvum} on growth by age of infection and prior nutritional status. Therefore, we are not able to separate the effect of age of infection on catch-up from that of stunting prior to infection.

Results from this study demonstrate that \textit{C. parvum} infection not only caused acute growth retardation in infants and children, but also that height and weight did not return to normal until several months after infection. Younger children infected with \textit{C. parvum} took longer to recover from the nutritional insult of the infection than did older children. This difference may occur for the following reasons: 1) younger children may have less developed digestive systems, which may be less efficient to metabolize and transport nutrients; and 2) younger children may be less capable of responding to infection, perhaps because of immunologic deficiencies and, consequently, they may have sustained more severe intestinal damage or have taken longer to recover from the infection (31, 32). Studies of individuals with acquired immunodeficiency syndrome (AIDS) have suggested that cryptosporidiosis is associated with intestinal damage and malabsorption (33). The mechanism of growth retardation we observed in children infected with \textit{C. parvum} may be similar, while less acute, to that operating in AIDS-related cryptosporidiosis.

The Peruvian population exhibits a high degree of nutritional stunting: 37 percent of children under age 5 years are stunted (34). The effects of \textit{C. parvum} infection on growth and especially the lasting effects on height are likely contributors to the prevalence of stunting in Peru. Furthermore, the magnitude and persistence of this effect is intensified for children with poorer nutritional status. The synergy between the effects of \textit{C. parvum} and prior stunting on growth underscores the need for aggressive community-based interventions, such as nutritional rehabilitation programs, to reduce the burden of stunting in developing countries.

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