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Early enteropathogenic *E. coli* infections associated with growth faltering at 24 months of age in urban Bangladesh

Michael B. Arndt[1,2], Patricia B. Pavlinac[2], Barbra A. Richardson[2,3], Tahmeed Ahmed[4], Mustafa Mahfuz[4], Rashidul Haque[5], Grace C. John-Stewart[2,6,7,8,9], Donna M. Denno[2,8,10], Judd L. Walson[2,6,7,9,10]

[1]PATH; [2]University of Washington (UW) Department of Global Health; [3]UW Department of Biostatistics; [4]icddr,b Nutrition and Clinical Services Division; [5]icddr,b Parasitology Laboratory; [6]UW Department of Medicine; [7]UW Medicine Division of Allergy and Infectious Diseases; [8]UW Department of Pediatrics; [9]UW Department of Epidemiology; [10]Childhood Acute Illness & Nutrition Network, Nairobi, Kenya

Introduction

- *Escherichia coli* (*E. coli*) are among the first microbes to colonize the infant gut.
- *E. coli* pathotypes—heat-labile enterotoxigenic (LT-ETEC) or heat-stable enterotoxigenic (ST-ETEC), typical and atypical enteropathogenic (tEPEC and aEPEC), enteroaggregative (EAEC), enteroinvasive (EIEC), and Shiga-toxin producing (STEC)—are among the leading causes of child diarrhea globally.
- Early-life enteropathogen exposure has been associated with child stunting in low-resource settings; however, the contribution of pathogenic *E. coli* has not been well characterized.

Objective

Describe the frequency of pathogenic *E. coli* infection from birth to 6 months of age in urban Bangladesh, and identify strains associated with linear growth at 24 months of age.

Methods

Study population

- 265 healthy newborns from an urban slum in Dhaka, Bangladesh, were enrolled into The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health (MAL-ED) cohort within the first 17 days of life.

Data collection

- Assessment of household and maternal information was done at enrollment, and child anthropometry was assessed at monthly intervals.
- Children were weighed using metric pediatric balances with a certified accuracy of 100 g, and length was measured using a marked platform with a sliding footboard.
- Stools were collected monthly through 1 year of age from infants without diarrhea, and during diarrhea episodes.
- *E. coli* isolates were identified using conventional stool culture, and virulence genes were detected by multiplex polymerase chain reaction.
- Our focus was on *E. coli* detected during the first 6 months, the period where infants could first be exposed to enteropathogen infection(s).

Statistical methods

- Linear regression was used to test the relationship(s) between detection of *E. coli* in the first 6 months of life and length for age z-score (LAZ) at age 24 months.
- All models were adjusted for covariates chosen a priori, listed in Table 1.

Table 1. Exposures, outcomes, and covariates.

Exposure	***E. coli* pathotypes**	tEPEC aEPEC EAEC LT-ETEC ST-ETEC
Outcome	**Linear growth**	Attained LAZ at age 24 months
Covariates	**Size at birth**	LAZ at birth
	Diarrhea	Diarrhea episodes in the first 6 months
	Breastfeeding	Infant exclusively breastfed for 100 days
	Maternal body mass index	Mother's mass/height^2

Population characteristics

210 of 265 children were followed to 2 years of age and had at least one nondiarrheal stool collected in the first 6 months.

Table 2. Characteristics of participants at enrollment (N= 210).

			n (%) or median (interquartile range)
Infant	Sex	Female	102 (48.6)
	Anthropometry	LAZ	-0.93 (-1.60, -0.30)
		Stunting (LAZ < -2)	32 (15.2)
		WAZ	-1.22 (-1.88, -0.57)
		WHZ	-0.94 (-1.68, -0.39)
Mother		Age (years)	25 (21, 28)
	Anthropometry	Height (cm)	149 (146, 153)
		Weight (kg)	48.8 (43.1, 56.0)
		Body mass index	21.8 (19.7, 24.7)
	Marital status	Married (polygamous)	29 (13.8)
	Education	Never attended school	41 (19.5)

Results

- Among the 210 children, 89% had at least one *E. coli* pathotype identified in their stool in the first 6 months of life.
- Overall, the most commonly detected pathotypes were EAEC (79%) and tEPEC (22%).
- For all pathotypes, detection in nondiarrheal samples was more common than in diarrheal samples. However, this observation may be due to more nondiarrheal than diarrheal (n= 1,383 vs. n= 345) stools with *E. coli* testing.
- This was especially true for EAEC (75% versus 30%), aEPEC (11% versus 3%), and ST-ETEC (15% versus 6%).

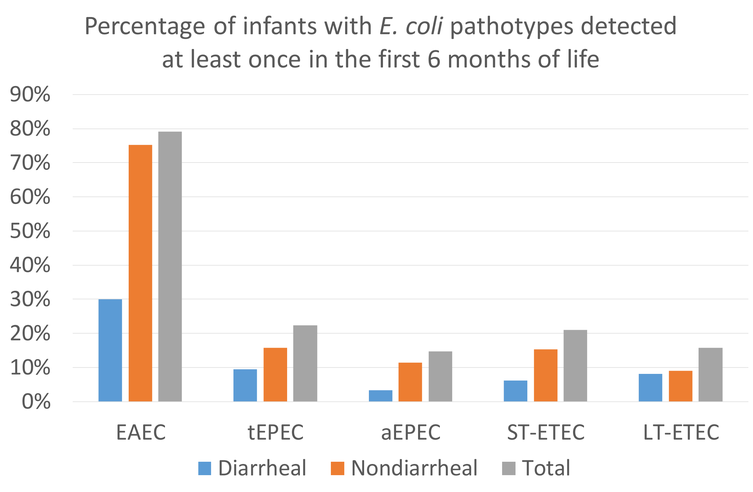

Table 3. Associations between EAEC, tEPEC, aEPEC, ST-ETEC, and LT-ETEC detected in months 0 t0 6 and LAZ at 24 months of age.[*]

	Diarrheal Coeff. (95% CI)	**Nondiarrheal** Coeff. (95% CI)	**All detections** Coeff. (95% CI)
EAEC	-0.034 (-0.294, 0.227)	-0.187 (-0.439, 0.066)	-0.182 (-0.430, 0.066)
tEPEC	-0.264 (-0.657, 0.128)	-0.482‡ (-0.786, -0.177)	-0.409‡ (-0.670, -0.149)
aEPEC	-0.310 (-0.962, 0.341)	0.182 (-0.136, 0.500)	0.076 (-0.218, 0.370)
ST-ETEC	-0.119 (-0.596, 0.358)	-0.134 (-0.444, 0.176)	-0.159 (-0.437, 0.120)
LT-ETEC	-0.291 (-0.710, 0.128)	-0.299 (-0.700, 0.101)	-0.375† (-0.702, -0.048)

Note: CI, confidence interval; Coeff, coefficient.
[*]All models adjusted for LAZ at birth, maternal body mass index, diarrhea episodes in the first 6 months, and exclusive breastfeeding maintained through the first 100 days.
† p-value < 0.05.
‡ p-value < 0.01.

Results (continued)

- In single pathotype models (Table 3), tEPEC and LT-ETEC detection in any stool sample were both negatively associated with LAZ at 24 months of age.
- In a multipathotype model (Table 4), the mean LAZ at 24 months was 0.371 lower in children with tEPEC detected in any stool (p=0.006) than in those without and 0.314 lower in children with LT-ETEC detected than in those without (p=0.060), but this was not significant.
- In both single and multipathotype models restricted to nondiarrheal stools, only tEPEC detection was significantly associated with LAZ at 24 months.

Table 4. Associations between tEPEC and LT-ETEC (shared model) detected in months 0 to 6 and LAZ at 24 months of age.[*]

	Diarrheal Coeff. (95% CI)	**Nondiarrheal** Coeff. (95% CI)	**All detections** Coeff. (95% CI)
tEPEC	-0.261 (-0.653, 0.130)	-0.459† (-0.760, -0.158)	-0.371† (-0.635, -0.107)
LT-ETEC	-0.288 (-0.706, 0.131)	-0.224 (-0.588, 0.140)	-0.314 (-0.641, 0.014)

Note: CI, confidence interval; Coeff, coefficient.
[*]All models adjusted for LAZ at birth, maternal body mass index, diarrhea episodes in the first 6 months, and exclusive breastfeeding maintained through the first 100 days
† p-value< 0.01

Conclusions

- Early tEPEC and LT-ETEC infections were significantly associated with growth faltering at 2 years of age in children in urban Bangladesh.
- Early tEPEC infections are associated with poor child growth even in the absence of diarrhea.
- Absence of a significant association between nondiarrheal LT-ETEC and growth faltering may be due to insufficient power.
- Novel prevention and treatment interventions targeting tEPEC and LT-ETEC may need to focus on children in the first 6 months of life in order to address growth faltering attributable to *E. coli*.

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