PROVIDE Study

(Performance of Rotavirus and Oral Polio Vaccines in Developing Countries)

Final Report and Annotated Bibliography

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**Goal**

Define the environmental stresses that impair infant growth,

vaccination and neurocognitive development

**Key Message**

Independent Environmental Drivers of Child Morbidity are:

(1) Environmental enteric dysfunction (EED), measured noninvasively by gut inflammation.

(2) Systemic inflammation, measured by IL-1, TNF- and ferritin.

(3) Maternal health and birth weight and length.

Combined, these environmental factors account for 46% of variance in change in HAZ over the

1st year of life and 24% of variance in Rotarix-induced 18 week plasma IgA).

**What We Have Learned**

**Oral Polio Vaccine Failure**

• OPV failure was associated with:

(i) enterovirus and campylobacter infection at the time of vaccination8,

(ii) environmental enteric dysfunction (EED)15;

(iii) systemic inflammation15; and

(iv) maternal height and education15.

• IPV substitution for the 4th dose of tOPV provided superior humoral, and similar intestinal immunity3.

• Substitution of bOPV for tOPV created a gap in mucosal immunity to type 2 poliovirus5.

• Oral polio vaccination was associated with nonspecific protection from diarrheal disease, suggesting that replacement of oral with inactivated polio vaccination in the future may lead to an increase in diarrheal disease6.

**Rotarix Vaccine Failure:**

•.Rotarix failure was associated with:

(i) enterovirus infection at the time of vaccination8,

(ii) environmental enteric dysfunction (EED)15;

(iii) systemic inflammation15; and

(iv) maternal education15.

(v) male sex15.

• Risk factors for rotavirus diarrhea (in both vaccinated and non-vaccinated infants) include low serum zinc7, well nourishment9, maternal rotavirus antibody12 and blood group secretor phenotype13.

**Environmental Enteric Dysfunction (EED):**

• Only certain enteropathogens were associated with EED:

(i) *Cryptosporidium, Campylobacter jejuni/coli* and *Shigella/EIEC* diarrhea were the only causes of diarrhea associated with the development of stunting22

(ii) *Campylobacter jejuni/coli* and *Shigella/EIEC* diarrhea were the only causes of diarrhea associated with inflammation (as measured by C reactive protein)22.

• Microbiota immaturity was associated with stunting and severe acute malnutrition14.

• Small Intestine Bacterial Overgrowth (SIBO) measured by hydrogen breath testing was associated with stunting17.

• EED was present in 80% of children at 6-12 weeks of age as measured by fecal biomarkers of inflammation15.

**Metabolomics, Epigenetics and Malnutrition:**

• Metabolomics demonstrated that gut microbiota dysbiosis was associated with a reduced capacity of the gut microbiome to synthesize essential amino acids, and that malnourished children had lower levels of essential amino acids in plasma23.

• Epigenetic changes (histone H3 lysine 4 trimethylation) emerged over the first year of life and involved a global decrease in methylation at canonical locations near gene start sites and increased methylation at ectopic sites throughout the genome25.

**Neurocognitive Development and EED**

• Systemic inflammatory markers and febrile illness early in life were significantly associated with poor neurodevelopmental outcomes20,26,27. Conversely a type 2 anti-inflammatory response was associated with a better neurodevelopmental outcome26.

• Malnutrition at birth (stunted and underweight) was also associated with a worse neurocognitive outcome20.

**EED and Wheezing**

• Wheezing in the first year of life was predicted by systemic inflammation early in life, poverty, and male sex28.

**On-going Research**

• Design of a maternal nutritional supplement with Perrigo Nutritionals, Inc. (Bill Petri – UVa, Cindy Barber – Perrigo, Inc. and Tahmeed Ahmed – icddr,b)

• Enteropathogens associated with vaccine failure, stunting, wheezing and cognitive impairment (Bill Petri & Eric Houpt - UVa)

• Correlates of Rotarix protection (Beth Kirkpatrick - UVM & Bill Petri – UVa)

• Neurostructural tests of child development (Chuck Nelson – Harvard Bill Petri – UVa)

• T cell senescence in infants in Dhaka vs Palo Alto (Mark Davis – Stanford & Bill Petri – UVa)

• Epigenetics of malnutrition as measured by histone tail modifications (David Auble - UVa)

• Metabolomic and metagenomic signature of malnutrition (Bill Petri – UVa, Jens Nielsen – Chalmers, Rob Knight - UCSD)

**Child Health Outcomes Measured**

Growth from birth to 5 years of age.

EPI Vaccine response.

Neurocognitive development (Bayley’s, Mullens and WPPSI tests, EEG, fNIRS, fMRI)

**Biorepository and Database**

Database has 192 tables containing 4.5 million records.

Biorepository of breast milk, stool and urine from children from birth to 5 years of age.

GWAS and HLA typing for every child

**Vision for the Future of PROVIDE**

PROVIDE we propose as the site for a multi-intervention approach to improving child health. The focus will be correction of the three environmental contributors to infant morbidity and mortality. The PROVIDE investigative team and the families of Mirpur Dhaka bring tremendous intellectual resources, interdisciplinary science, community good will, and a proven track record of discovery from tightly run clinical trials with superb data management.

PROVIDE data management allows real-time sharing with the Foundation. It has the in-field ability to monitor and assess prenatal health, gestational through fetal ultrasound, enteric infections through TAC PCR, breast milk fatty acid composition, microbiome maturity, vaccine response measures, and immunophenotyping via CyTOF. The PROVIDE clinic and study office has on-site testing for neurodevelopment (fMRI, EEG, fNIRS, eye tracking, Bayley’s WPPSI), and a highly capable team trained in good clinical practices.

**PROVIDE Annotated Bibliography**

**Polio Vaccine Failure**

**1.** Haque R, Snider C, Liu Y, Ma J, Liu L, Nayak U, Mychaleckyj J, Korpe P, Mondal D, Kabir M, Alam M, Pallansch M, Oberste MS, Weldon W, Kirkpatrick B, Petri WA Jr. Oral Polio Vaccine Response in Breast Fed Infants with Malnutrition and Diarrhea. Vaccine 32:478– 482, 2014. PMID: 24300591. *Diminished serum neutralizing response to OPV, but not failure of intramuscularly administered vaccines, was associated with malnutrition, diarrhea, and shorter breastfeeding duration (****preliminary data from earlier birth cohort used for grant application****)*

2. **Taniuchi M, Begum S, Uddin MJ, Platts-Mills JA, Liu J, Kirkpatrick BD, Chowdhury AH, Jamil KM, Haque R, Petri WA Jr, Houpt ER.** Kinetics of polio shedding following oral vaccination as measured by qRT-PCR versus culture. J Clin Microbiol, 53:206-11, 2015. PMID: 25378579. *An RT-qPCR assay for OPV can simply and quantitatively detect all three Sabin strains directly in stool samples to approximate shedding both qualitatively and quantitatively.*

3. Mychaleckyj JC, Haque R, Carmolli M, Zhang D, Colgate ER, Nayak U, Taniuchi M, Dickson D, Weldon WC, Oberste MS, Zaman K, Houpt ER, Alam M, Kirkpatrick BD, Petri WA Jr. Effect of substituting IPV for tOPV on immunity to poliovirus in Bangladeshi infants: An open-label randomized controlled trial. Vaccine 34:358–366, 2016. PMID: 26643930. *In the Bangladesh PROVIDE Cohort IPV substitution for the 4th dose of tOPV provided superior humoral immunity and similar intestinal immunity. The IPV-modified regimen may be considered for vaccination programs without loss of intestinal immunity.*

4. Kanungo S, Kim DR, Haldar B, Snider C, Nalavade U, Kim SA, Park JY, Sinha A, Mallick AH, Manna B, Sur D, Nandy RK, Deshpande JM, Czerkinsky C, Wierzba TF, Petri WA Jr, Ali M, Dey A. Comparison of IPV to tOPV week 39 boost of primary OPV vaccination in Indian infants: an open labelled randomized controlled trial. Heliyon. 2017 Jan 9;3(1):e00223. doi:10.1016/j. heliyon.2016.e00223. eCollection 2017 Jan.PMID: 28194449. *In the India PROVIDE Cohort an IPV boost at week 39 was equivalent to tOPV in intestinal immunity, and provided higher seroconversion compared to tOPV. IPV for OPV boost should prove to be a step forward in the global polio eradication initiative to reduce the problem of circulating vaccine-derived poliovirus.*

5. Taniuchi M, Famulare M, Zaman K, Uddin MJ, Upfill-Brown AM, Ahmed T, Saha P, Haque R, Bandyopadhyay AS, Modlin JF, Platts-Mills JA, Houpt ER, Yunus M, Petri WA Jr. Community transmission of type 2 poliovirus after cessation of trivalent oral polio vaccine in Bangladesh: an open-label cluster-randomised trial and modelling study. Lancet Infect Dis. 2017 Oct;17(10):1069-1079. doi: 10.1016/S1473-3099(17)30358-4. Epub 2017 Jul 7. PMID: 28693854 *In this study, simulating 1 year of tOPV cessation, Sabin 2 transmission was higher in household contacts of mOPV2 recipients in villages receiving bOPV and either one or two doses of IPV. The study demonstrated the mucosal immunity gap to OPV2 in children receiving bOPV immunization.*

6. Upfill-Brown A, Taniuchi M, Platts-Mills JA, Kirkpatrick B, Burgess SL, Oberste MS, Weldon W, Houpt E, Haque R, Zaman K, Petri WA Jr. Nonspecific Effects of Oral Polio Vaccine on Diarrheal Burden and Etiology Among Bangladeshi Infants. Clin Infect Dis. 2017 Aug 1;65(3):414-419. doi: 10.1093/cid/cix354. PMID: 28444240. *Following vaccination with trivalent oral polio vaccine (tOPV) infants were randomly assigned to receive tOPV (n = 315) or inactivated polio vaccine (IPV) (n = 299) at 39 weeks. Episodes of diarrhea were documented through clinic visits and twice-weekly house visits through 52 weeks. The number of days with diarrhea (P = .0037) were lower in the OPV arm. Our results suggest that OPV may cause nonspecific reductions in mortality, as has been studied elsewhere, by reducing etiology-specific diarrheal burden.*

**Rotavirus Vaccine Failure**

7. Colgate ER, Haque R, Dickson DM, Carmolli MP, Mychaleckyj JC, Nayak U, Qadri F, Alam M, Walsh MC, Diehl SA, Zaman Z, Petri WA Jr, Kirkpatrick BD. Delayed Dosing of Oral Rotavirus Vaccine Demonstrates Decreased Risk of Rotavirus Gastroenteritis Associated With Serum Zinc: A Randomized Controlled Trial. Clin Infect Dis 63:634-41, 2016. PMID:27217217 *Rotarix post-vaccination efficacy against severe rotavirus diarrhea was higher than anticipated at 73.5% using delayed dosing. Serum zinc and family income were associated with protection from rotavirus diarrhea independent of vaccination.*

8. Taniuchi M, Platts-Mills JA, Begum S, Uddin MJ, Sobuz SU, Liu J, Colgate ER, Carmolli MP, Dickson DM, Nayak U, Kirkpatrick BD, Haque R, Petri WA Jr, Houpt ER. Impact of Enterovirus and Other Enteric Pathogens on Oral Polio and Rotavirus Vaccine Performance in Bangladeshi Infants. Vaccine 34:3068-75, 2016. PMID: 27154394. *Campylobacter and enterovirus infection at the time of administration of the first dose of OPV was associated with lower OPV1-2 serum neutralizing titers, while enterovirus quantity was also associated with diminished rotavirus IgA vaccine response.*

9. Verkerke H, Sobuz S, Ma JZ, Petri SE, Reichman D, Qadri F, Rahman M, Haque R, Petri WA Jr. Malnutrition Is Associated with Protection from Rotavirus Diarrhea: Evidence from a Longitudinal Birth Cohort Study in Bangladesh. J Clin Microbiol 54:2568-74, 2016. PMID: 27510830. *We observed that common measures of healthy growth and development were positively associated with a risk of symptomatic rotavirus infection. This finding runs counter to the idea that improving childhood nutrition will implicitly decrease the incidence of symptomatic infection by enteric pathogens. As childhood nutrition improves worldwide, rotavirus infection may remain a public health challenge, making universal vaccination of even greater importance.*

10. Sinha A, Kanungo S, Kim DR, Manna B, Song M, Park JY, Haldar B, Sharma P, Mallick AH, Kim SA, Babji S, Sur D, Kang G, Ali M, Petri WA Jr, Wierzba TF, Czerkinsky C, Nandy RK, Dey A. Antibody secreting B cells and plasma antibody response to rotavirus vaccination in infants from Kolkata India. Heliyon. 2018 Feb 1;4(1):e00519. doi: 10.1016/j.heliyon.2018.e00519. PMID: 29560435. *We evaluated circulating antibody-secreting cells (ASCs) as a potential means to evaluate mucosal immune responses to rotavirus vaccine. Total blood IgA-ASC responses were detected in 26.4% of subjects who were non-responders before vaccination.*

11. Rogawski ET, Platts-Mills JA, Colgate ER, Haque R, Zaman K, Petri WA, Kirkpatrick BD. Quantifying the Impact of Natural Immunity on Rotavirus Vaccine Efficacy Estimates: A Clinical Trial in Dhaka, Bangladesh (PROVIDE) and a Simulation Study. J Infect Dis. 2018 Mar 5;217(6):861-868. doi: 10.1093/infdis/jix668. PMID: 29514306 *We compared the PROVIDE original per-protocol Rotarix vaccine efficacy to efficacy derived from a survival model in which children were considered immune after their first rotavirus diarrhea episode. Accounting for naturally acquired immunity increased efficacy against severe rotavirus diarrhea from 63% to 70%.*

12. Lee B, Carmolli M, Dickson DM, Colgate ER, Diehl SA, Uddin MI, Islam S, Hossain M, Rafique TA, Bhuiyan TR, Alam M, Nayak U, Mychaleckyj JC, McNeal MM, Petri WA Jr, Qadri F, Haque R, Kirkpatrick BD. Rotavirus-specific IgA Responses Are Impaired and Serve as a Sub-Optimal Correlate of Protection among Infants in Bangladesh. Clin Infect Dis. 2018 Jan 31. doi: 10.1093/cid/ciy076. PMID: 29394355. *Increased RV-specific maternal antibodies significantly impaired immunogenicity. Seroconversion was associated with reduced risk of RVD through one year of life, but RV-IgA seropositivity only explained 7.8% of the vaccine effect demonstrated by the clinical endpoint (RVD).*

13. Lee B, Dickson DM, deCamp AC, Ross Colgate E, Diehl SA, Uddin MI, Sharmin S, Islam S, Bhuiyan TR, Alam M, Nayak U, Mychaleckyj JC, Taniuchi M, Petri WA Jr, Haque R, Qadri F, Kirkpatrick BD. Histo-Blood Group Antigen Phenotype Determines Susceptibility to Genotype-Specific Rotavirus Infections and Impacts Measures of Rotavirus Vaccine Efficacy. J Infect Dis. 2018 Apr 11;217(9):1399-1407. doi: 10.1093/infdis/jiy054. PMID: 29390150. *Rotarix protected secretors and non-secretors similarly from rotavirus diarrhea. However. unvaccinated non-secretors had a reduced risk of RVD (RR 0.53, 95% CI 0.36-0.79) mediated by complete protection from P[4] but not P[8] RVs. We concluded that HBGA status may impact VE estimates by altering susceptibility to RV in unvaccinated children; future trials should therefore account for HBGA status.*

**Environmental Enteric Dysfunction (EED)**

14. Subramanian S, Huq S, Yatsunenko T, Haque R, Mahfuz M, Alam MA, Benezra A, DeStefano J, Meier MF, Muegge BD, Barratt MJ, VanArendonk LG, Zhang Q, Province MA, Petri WA Jr, Ahmed T, Gordon JI. Persistent gut microbiota immaturity in malnourished Bangladeshi children. Nature 510:417-21, 2014. PMID: 24896187 *Microbiota maturity indices provide a microbial measure of human postnatal development, a way of classifying malnourished states, and a parameter for judging therapeutic efficacy. Severe acute malnutrition is associated with significant relative microbiota immaturity that is only partially ameliorated following two widely used nutritional interventions.*

15. Naylor C, Lu M, Haque R, Mondal D, Buonomo E, Nayak U, Mychaleckyj J, Kirkpatrick BD, Colgate ER, Carmolli M, Dickson D, van der Klis F, Weldon W, Oberste MS, PROVIDE study teams, Ma J, Petri WA Jr. Environmental Enteropathy, Oral Vaccine Failure and Growth Faltering in Infants in Bangladesh. EBioMedicine 2(11): 1759–1766, 2015. PMID: 26870801 *EED was present in 80% of children as measured by fecal biomarkers of inflammation. EED was associated with oral vaccine failure but not failure of systemically administered vaccines such as DTP. Biomarkers of EED and maternal health accounted for 46% of the variation in delta HAZ and 24% of rotavirus failure.*

16. Wagner VE, Dey N, Guruge J, Hsiao A, Ahern PP, Semenkovich NP, Blanton LV, Cheng J, Griffin N, Stappenbeck TS, Ilkayeva O, Newgard CB, Petri W, Haque R, Ahmed T, Gordon JI. Effects of a gut pathobiont in a gnotobiotic mouse model of childhood undernutrition. Sci Transl Med. 8(366):366ra164, 2016. PMID: 27881825 *Pathobiont-associated cachexia in a gnotobiotic model of childhood undernutrition is determined by strain-level interactions within the gut microbiota.*

17. Donowitz JR, Haque R, Kirkpatrick BD, Alam M, Lu M, Kabir M, Kakon SF, Islam BZ, Afreen S, Musa A, Khan SS, Colgate ER, Carmolli MP, Ma JZ, Petri WA Jr. Small Intestine Bacterial Overgrowth and Environmental Enteropathy in Bangladeshi Children. mBio 7: e02102-15, 2016. PMID: 26758185. *SIBO was present in 16.7% (15/90) of two-year old children. The strongest predictors of SIBO were decreased length-for-age Z score since birth and an open sewer outside the home. The markers of intestinal inflammation, fecal Reg1β and calprotectin, were elevated in SIBO positive children. We concluded that linear growth faltering and poor sanitation are associated with SIBO and that SIBO is associated with intestinal inflammation.*

18. Korpe PS, Haque R, Gilchrist C, Valencia C, Niu F, Lu M, Ma JZ, Petri SE, Reichman D, Kabir M, Duggal P, Petri WA Jr. Natural History of Cryptosporidiosis in a Longitudinal Study of Slum-Dwelling Bangladeshi Children: Association with Severe Malnutrition. PLoS Negl Trop Dis. 2016 May 4;10(5):e0004564. doi: 10.1371/journal.pntd.0004564. eCollection 2016 May. PMID: 27144404. *This longitudinal birth cohort study of 392 slum-dwelling Bangladeshi children showed in the first two years of life that 77% of children experienced at least one infection with Cryptosporidium spp. and these infections were significantly associated with stunting of children’s growth by two years of age.*

19. Nayak U, Kanungo S, Zhang D, Ross Colgate E, Carmolli MP, Dey A, Alam M, Manna B, Nandy RK, Kim DR, Paul DK, Choudhury S, Sahoo S, Harris WS, Wierzba TF, Ahmed T, Kirkpatrick BD, Haque R, Petri WA Jr, Mychaleckyj JC. Influence of maternal and socioeconomic factors on breast milk fatty acid composition in urban, low-income families. Matern Child Nutr. 2017 Oct;13(4). doi: 10.1111/mcn.12423. Epub 2017 Feb 15. PMID: 28198164. *Socioeconomic factors of maternal education and household prosperity were associated with breast milk lipid composition, indicating a potential area for nutritional intervention for infant nutrition by supplementing the diet of mothers.*

20. Donowitz JR, Cook H, Alam M, Tofail F, Kabir M, Colgate ER, Carmolli MP, Kirkpatrick BD, Nelson CA, Ma JZ, Haque R, Petri WA Jr. Role of maternal health and infant inflammation in nutritional and neurodevelopmental outcomes of two-year-old Bangladeshi children. PLoS Negl Trop Dis. 2018 May 29;12(5):e0006363. doi: 10.1371/journal.pntd.0006363. eCollection 2018 May. PMID: 29813057. *Birth anthropometry and maternal weight were strong predictors of growth while enteric and systemic inflammation had stronger associations with neurodevelopment. These data suggest that further study of stunting in low-income settings should include variables relating to maternal and prenatal health, while study targeting neurodevelopmental outcomes should additionally target causes of systemic and enteric inflammation.*

21. Schnee AE, Haque R, Taniuchi M, Uddin MJ, Petri WA Jr. Evaluation of Two New Membrane-based and Microtiter Plate Enzyme-linked Immunosorbent Assays for the detection of Campylobacter jejuni in stool of Bangladeshi children. J Clin Microbiol. 2018 Jun 20. pii: JCM.00702-18. doi: 10.1128/JCM.00702-18. PMID: 29925645. *Two new monoclonal antibody-based, sandwich EIA assays for fecal antigen detection of Campylobacter jejuni or Campylobacter coli were evaluated using diarrheal stool specimens from a cohort of children in Bangladesh. The QUIK CHEK™ rapid EIA and the CHEK™ ELISA tests had a sensitivity of 95.7% (specificity 97% and 96%, respectively), supporting their usefulness in diagnosis of Campylobacter diarrhea.*

22. Schnee AE, Haque R, Taniuchi M, Uddin J, Alam M, Liu J, Rogawski ET, Kirkpatrick B, Houpt ER, Petri WA Jr, Platts-Mills JA. Identification of etiology-specific diarrhea associated with linear growth faltering in Bangladeshi infants. Am J Epidemiol. 2018 May 15. doi: 10.1093/aje/kwy106. PMID: 29767678. *There was no relationship between all-cause diarrhea and length at 12 months. However, Cryptosporidium, Campylobacter jejuni/coli, and Shigella/enteroinvasive E. coli (EIEC) diarrhea were associated with linear growth deficits. C. jejuni/coli and Shigella/EIEC attributable diarrhea were associated with elevated CRP. These findings demonstrate that the relationship between diarrhea and linear growth is pathogen specific, reinforcing the need for pathogen-specific interventions.*

23. Kumar M, Boyang J, Babaei P, Das P, Lappa D, Ramakrishnan G, Fox TE, Haque R, Petri WA, Bäckhed F, Nielsen J. Gut microbiota dysbiosis is associated with malnutrition and reduced plasma amino acid levels: Lessons from genome-scale metabolic modeling. [Metab Eng.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Gut+microbiota+dysbiosis+is+associated+with+malnutrition+and+reduced+plasma+amino+acid+levels%3A+Lessons+from+genome-scale+metabolic+modeling) 2018 Sep;49:128-142. PMID: 30075203. *Mathematical modeling of the metabolic capabilities of the gut microbiome from malnourished vs healthy children in Bangladesh and Malawi demonstrated a reduced capacity for the synthesis of essential amino acids. Targeted plasma metabolic profiling of 25 healthy and 25 malnourished children over the first two years of life confirmed that stunted children had reduced plasma levels of essential amino acids. These analyses provide a framework towards understanding the contribution of the microbiome to malnutrition.*

24. Mychaleckyj JC, Nayak U, Colgate ER, Zhang D, Carstensen T, Ahmed S, Ahmed T, Mentzer AJ, Alam M, Kirkpatrick BD, Haque R, Faruque ASG, Petri WA Jr. Multiplex genomewide association analysis of breast milk fatty acid composition extends the phenotypic association and potential selection of FADS1 variants to arachidonic acid, a critical infant micronutrient. J Med Genet. 2018 Jul;55(7):459-468. doi: 10.1136/jmedgenet-2017-105134. PMID: 29514873 *Arachidonic acid concentration in breast milk was influenced by genetic variation in the fatty acid desaturase genes at the FADS1/2/3 locus, potentially affecting infant growth or cognition.*

25. Uchiyama R, Shetty SJ, Linford AS, Pray-Grant M, Wagar L, Davis M, Haque R, Gaultier A, Mayo MW, Grant PA, Petri WA Jr, Bekiranov S, and Auble DT. Histone methylation signature associated with undernutrition. [Proc Natl Acad Sci U S A.](https://www.ncbi.nlm.nih.gov/pubmed/30420518) 2018 Nov 27;115(48):E11264-E11273. doi: 10.1073/pnas.1722125115. PMID: 30420518 *A pattern of chromatin modification in blood cells of stunted children emerged over time and involves a global decrease in methylation at canonical locations near gene start sites and increased methylation at ectopic sites throughout the genome.*

**Neurocognitive Development and EED**

26. Jiang NM, Tofail F, Moonah SN, Scharf RJ, Taniuchi M, Ma JZ, Hamadani JD, Houpt ER, Azziz-Baumgartner E, Haque R, Petri WA Jr. Febrile illness and pro-inflammatory cytokines are associated with lower neurodevelopmental scores in Bangladeshi infants living in poverty. BMC Pediatrics 14:50 DOI: 10.1186/1471-2431-14-50 URL: <http://www.biomedcentral.com/1471-2431/14/50>, 2014. *Every additional 10 days of fever was associated with a 1.9 decrease in language composite score and a 2.1 decrease in motor composite score. Elevated levels of the pro-inflammatory cytokines IL-1β and IL-6 were significantly associated with a 4.9 and 4.3 decrease in motor score, respectively. Conversely, an elevated level of the Th-2 cytokine IL-4 was associated with a 3.6 increase in cognitive score (all p < 0.05). These findings suggest that markers of inflammation could serve as prognostic indicators and potentially lead to immune-based therapies to prevent developmental delays in at-risk children.*

27. Jiang NM, Tofail F, Ma JZ, Haque R, Kirkpatrick B, Nelson CA, Petri WA. Early Life Inflammation and Neurodevelopmental Outcome in Bangladeshi Infants Growing Up in Adversity. Am J Trop Med Hyg. 2017 Sep;97(3):974-979. doi: 10.4269/ajtmh.17-0083. PMID: 28722635.  
*Systemic inflammatory markers (sCD14 and CRP) were significantly associated with poor neurodevelopmental outcomes. The cumulative number of CRP elevations that a child experienced in the first year of life, as well as IL-1β and IL-6 at 18 weeks of age, were also negatively associated with Bayley Scales results. CRP, sCD14, IL-1β, and IL-6 were associated with lower neurodevelopmental outcomes. Our findings implicate a role of inflammation in the neurodevelopment of children growing up in adversity.*

**EED and Wheezing**

28. Burgess SL, Lu M, Ma JZ, Naylor C, Donowitz JR, Kirkpatrick BD, Haque R, Petri WA Jr. Inflammatory markers predict episodes of wheezing during the first year of life in Bangladesh. Respiratory Medicine 110:53-57, 2016. PMID: 26631486. *Children from Dhaka, Bangladesh were recruited at birth and episodes of wheezing were measured alongside nutritional, immunological and socioeconomic factors over a one-year period. Poisson Regression with variable selection was utilized to determine what factors were associated with wheezing. Wheezing in the first year of life was predicted by systemic inflammation early in life, poverty, and male sex. These results support the hypothesis that there is a link between inflammation in infancy and the development of respiratory illness later in life and provide specific biomarkers that can predict wheezing in a low-income country.*

**Study Methodology and Analysis**

29. Kirkpatrick BD, Colgate ER, Mychaleckyj JC, Haque R, Dickson DM, Carmolli MP, Nayak U, Taniuchi M, Naylor C, Qadri F, Ma JZ, Alam M, Walsh MC, Diehl SA; PROVIDE Study Teams, Petri WA Jr. The "Performance of Rotavirus and Oral Polio Vaccines in Developing Countries" (PROVIDE) study: description of methods of an interventional study designed to explore complex biologic problems. Am J Trop Med Hyg 92:744–751, 2015. PMID: 25711607. *Methods for the enrollment and 2-year follow-up of a 700 child birth cohort are described,* *including core laboratory, safety, regulatory, and data management practices*

30. Lu M, Zhou J, Naylor C, Kirkpatrick BD, Haque R, Petri WA Jr, Ma JZ. Application of penalized linear regression methods to the selection of environmental enteropathy biomarkers. Biomark Res. 2017 Mar 9;5:9. doi: 10.1186/s40364-017-0089-4. eCollection 2017. PMID: 28293424 *Penalized linear regression methods are plausible alternatives to traditional variable selection methods, and the suggested methods are applicable to other biomedical studies. The selected early-stage biomarkers offer a potential explanation for the burden of malnutrition problems in low-income countries, allow early identification of infants at risk, and suggest pathways for intervention.*

31. Zhang Y, Zhou J, Niu F, Donowitz JR, Haque R, Petri WA Jr, Ma JZ. Characterizing early child growth patterns of height-for-age in an urban slum cohort of Bangladesh with functional principal component analysis. BMC Pediatr. 2017 Mar 21;17(1):84. doi: 10.1186/s12887-017-0831-y. *Growth modeling with the FPC1 and adj-FPC2 scores together were able to predict 90% of stunting at age 3, 4, and 5 years. Risk factors associated with such a change in growth included HAZ at birth (boys and girls), family income, family size, having an animal in the house and* *duration of exclusive breast-feeding (boys), and maternal weight, food coverage practice* *and source of household drinking water (girls)-* ***using data from earlier birth cohort study***

**Review Articles**

32. Korpe P, Petri WA Jr. Environmental Enteropathy: Critical implications of a poorly understood condition. Trends Molecular Medicine 2012, 18:328-336. PMID: 22633998

33. Donowitz JR, Petri WA Jr. Pediatric Small Intestinal Bacterial Overgrowth in Low-Income Countries. Trends Mol Med. 2015 21:6-15. doi: 10.1016/j.molmed.2014.11.001. PMID: 25486880

34. Petri WA Jr, Naylor C, Haque R. Environmental Enteropathy and Malnutrition: Do we know enough to intervene? BMC Med. 2014 Oct 14;12:187. doi: 10.1186/s12916-014-0187-1. PMID: 25604120

35. Gilmartin AA, Petri WA Jr. Exploring the role of environmental enteropathy in malnutrition, infant development and oral vaccine response. Philos Trans R Soc Lond B Biol Sci. 2015 Jun 19;370(1671). pii: 20140143. doi: 10.1098/rstb.2014.0143. PMID: 25964455

36. Watanabe, K, Petri WA Jr. Environmental Enteropathy: elusive but significant subclinical abnormalities in developing countries. EBioMedicine. 2016 Aug;10:25-32. doi: 10.1016/j.ebiom.2016.07.030. PMID: 27495791

37. Jiang NM, Cowan M, Moonah SN, Petri WA Jr. Impact of systemic inflammation on neurodevelopment. Trends Molecular Medicine 2018, 24:794-804. PMID: 30006148