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Department of Global Health | University of Washington

MATERNAL, NEONATAL, AND CHILD HEALTH DIGEST

UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS, RESEARCH & TRAINING (START) CENTER

REPORT TO THE BILL & MELINDA GATES FOUNDATION

MARCH 1, 2018

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LIST OF ARTICLES

OPTIMIZING BIRTH OUTCOMES FOR MOTHERS AND NEWBORNS

1. **GAS5 silencing protects against hypoxia/ischemia-induced neonatal brain injury.** {Abstract & START Commentary} {Full article}
    - Authors find a possible therapeutic approach for RNA-GAS5 in hypoxia/ischemia neonatal brain injury.

2. **Fetal growth restriction in rural Bangladesh: a prospective study.** {Abstract & START Commentary} {Full article}
    - Investigators took repeat measures of parameters during gestation and compared fetal growth to international reference growth charts.

3. **Association and birth prevalence of microcephaly attributable to Zika virus infection among infants in Paraíba, Brazil, in 2015–16: a case-control study.** {Abstract & START Commentary} {Full article}
    - Authors quantify the prevalence of microcephaly in Paraiba, Brazil and the proportion of cases attributable to Zika virus.

SUPPORT THRIVING IN THE COMMUNITY

4. **Similarities and differences in child development from birth to age 3 years by sex and across four countries: a cross-sectional, observational study.** {Abstract & START Commentary} {Full article}
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5. **Effects of water quality, sanitation, handwashing, and nutritional interventions on diarrhoea and child growth in rural Bangladesh: a cluster randomised controlled trial.** {Abstract & START Commentary} {Full article}
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6. **Effect of a mass radio campaign on family behaviours and child survival in Burkina Faso: a repeated cross-sectional, cluster-randomised trial.** {Abstract & START Commentary} {Full article}
    - Authors evaluated the effect of a mass radio campaign on all-cause post-neonatal under-5 mortality and all-cause under-5 mortality.

7. **Early childhood growth and cognitive outcomes: Findings from the MAL - ED study.** {Abstract & START Commentary} {Full article}
    - Authors examine how growth during the first 24 months of life is related to cognitive development.

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8. **Reagent Strips as an Aid to Diagnosis of Neonatal Meningitis in a Resource-limited Setting.** {Abstract & START Commentary} {Full article}
    - Authors find reagent strips to be reasonably accurate for diagnosing meningitis in neonates.

9. **Chitinase-3-like 1 is a biomarker of acute kidney injury and mortality in paediatric severe malaria.** {Abstract & START Commentary} {Full article}
    - Authors investigate the use of CHI3L1 as a biomarker for AKI complications in children with severe malaria.

CROSS-CUTTING

10. **Infant and child mortality in relation to malaria transmission in KEMRI/CDC HDSS, Western Kenya: validation of verbal autopsy.** {Abstract & START Commentary} {Full article}
    - Authors find verbal autopsy to have poor sensitivity and high specificity for identifying malaria as the cause of death in infants and children.

DETAILS OF ARTICLES

OPTIMIZING BIRTH OUTCOMES FOR MOTHERS AND NEWBORNS

1. GAS5 silencing protects against hypoxia/ischemia-induced neonatal brain injury
   Zhao RB, Zhu LH, Shu JP, Qiao LX, Xia ZK.
   Biochem Biophys Res Commun. 2018.
   PubMed ID. 29428721

ABSTRACT
Hypoxic/ischemic brain damage (HIBD) leads to high neonatal mortality and severe neurologic morbidity. However, the molecular mechanism of HIBD in the neonatal infant is still elusive. Long noncoding RNAs are shown as important regulators of brain development and many neurological diseases. Here, we determined the role of long noncoding RNA-GAS5 in HIBD. GAS5 expression was significantly up-regulated in hypoxic/ischemic-injured neonatal brain and hippocampal neurons. GAS5 silencing protected against hypoxic/ischemic-induced brain injury in vivo and primary hippocampal neuron injury in vitro. Mechanistically, GAS5 regulated hippocampal neuron function by sponging miR-23a. Intracerebroventricular injection of GAS5 shRNA significantly decreased brain GAS5 expression, reduced brain infarct size, and improved neurological function recovery. Collectively, this study suggests a promising therapeutic approach of GAS5 inhibition in the treatment of neonatal HIBD.

DOI: 10.1016/j.bbrc.2018.02.070
IMPACT FACTOR: 2.5
CITED HALF-LIFE: >10.0

START COMMENTARY: Findings from this study are of public health relevance as they suggest a possible new line of intervention for HIBD. Growth arrest-specific 5 (GAS5) is a long non-coding RNA that is involved in tunmorigenesis and vascular dysfunction. Long non-coding RNAs regulate gene expression at several levels (epigenetic, transcriptional, post-transcriptional) and have been shown to play a role in neurodegenerative diseases. This article investigated the role of RNA-GAS5 in HIBD using a rat pup model, to determine whether it may modulate neonatal HIBD. Authors found that GAS5 expression is up-regulated after rat pups were subjected to neonatal hypoxic/ischemic brain injury, primarily in the hippocampus, but also in the striatal and cortical regions. GAS5 expression was similarly upregulated when the primary hippocampal neurons were exposed to hypoxia or oxidative stress, suggesting that hypoxic/ischemic stress is what leads to GAS5 upregulation. They also found silencing GAS5 expression with si-RNA was protective against hypoxia-induced cell apoptosis and dead or dying cells for hippocampal neurons against hypoxic/ischemic stress in vitro. Rat pups with GAS5 knockdown had smaller brain infarct size, and better 8 week spatial learning, spatial memory and motor function than control rats following hypoxic/ischemic brain injury.

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2. Fetal growth restriction in rural Bangladesh: a prospective study
   Ferdous F, Rashid MH, Ma E, Raqib R, Hamada H, Wagatsuma Y.
   Trop Med Health.46(3). 2018 Feb.
   PubMed ID. 29445311

ABSTRACT
BACKGROUND: Fetal growth restriction (FGR) and low birth weight(LBW) are serious public health problems. In developing countries, the incidence of low birth weight is predominantly the result of FGR, and both low birth weight and FGR are associated with neonatal death and later growth and development. Fetal growth charts are important for assessing the size of the fetus during pregnancy. The aims of this study were to describe the fetal growth pattern of a population in rural Bangladesh where maternal undernutrition is prevalent and to compare the timing of FGR in that population with WHO and INTERGROWTH- 21st international reference values.
METHODS: From November 2001 to October 2003, pregnant women were recruited in Matlab, a sub district of Bangladesh, and underwent three follow-up ultrasound examinations during pregnancy for measurement of the parameters of the fetal head, abdomen, and femur. The data were fitted to a linear-cubic model, and the derived values were compared with international reference values.
RESULTS: A total of 2678 singleton pregnancies were included in the analyses. The mean (SD) maternal age was 25.9 (5.8) years (range, 14–47 years). The mean (SD) early pregnancy BMI was 20.1 (2.6) kg/m2 , and 27.6% of the women were underweight (BMI < 18.5 kg/m2). The growth of the biparietal diameter and abdominal circumference was significantly smaller throughout the pregnancy than the reference values ($P \leq 0.05$). Moreover, a larger deviation in the growth of Bangladeshi fetuses was observed after 28 weeks of gestation when compared with the WHO and INTERGROWTH-21st reference fetal growth charts ($P \leq 0.05$). After 28 weeks of gestation, the average Bangladesh estimated fetal weight gain per week of gestational age was significantly lower than the WHO estimated fetal weight by as much as 67.4 g ($P \leq 0.001$).
CONCLUSION: The present population-based study showed that fetuses were smaller in the third trimester when compared with the reference charts. Growth faltering started in the second trimester for all the biometric parameters for the head, abdomen, and femur. This finding provides more challenges concerning nutritional interventions.

DOI: 10.1186/s41182-018-0083-z
IMPACT FACTOR: 2.3
CITED HALF-LIFE: N/A

START COMMENTARY: Bangladesh has a high prevalence of maternal undernutrition and LBW; thus, it is important to understand the growth pattern of Bangladeshi fetuses, identify timing of growth faltering, and understand how well standard growth charts apply to the Bangladesh context. To do this, authors compared fetal growth, through repeat measures of parameters during gestation, to international reference growth charts. Figures 2 - 6 present the comparisons of each parameter to the international reference charts. Some strengths of this study are the large sample size, population-based design, and longitudinal fetal growth measurements. A limitation of this study is that the date of last menstrual period was accepted with more variability in the current study than in the international studies that were used to develop the standardized international growth charts. In addition, all the data came from one location in Bangladesh, which may limit generalizability due to differences in genetics and environmental exposures between populations.

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3. Association and birth prevalence of microcephaly attributable to Zika virus infection among infants in Paraíba, Brazil, in 2015–16: a case-control study
Krow-Lucal ER, Andrade MR, Cananéa JNA, Moore CA, Leite PL,Biggerstaff BJ, et al.
Lancet Child Adolesc Health. 2. 2018 March.
PubMed ID. N/A

ABSTRACT
BACKGROUND: In 2015, the number of infants born with microcephaly increased in Paraíba, Brazil, after a suspected Zika virus outbreak. We did a retrospective case-control investigation to assess the association of microcephaly and Zika virus.
METHODS: We enrolled cases reported to the national database for microcephaly and born between Aug 1, 2015, and Feb 1, 2016, on the basis of their birth head circumference and total body length. We identified controls from the national birth registry and matched them to cases by location, aiming to enroll a minimum of two controls per case. Mothers of both cases and controls were asked about demographics, exposures, and illnesses and infants were measured at a follow-up visit 1–7 months after birth. We took blood samples from mothers and infants and classified those containing Zika virus IgM and neutralizing antibodies as evidence of recent infection. We calculated prevalence of microcephaly and odds ratios (ORs) using a conditional logistic regression model with maximum penalized conditional likelihood, and combined these ORs with exposure probability estimates to determine the attributable risk.
FINDINGS: We enrolled 164 of 706 infants with complete information reported with microcephaly at birth, of whom we classified 91 (55%) as having microcephaly on the basis of their birth measurements, 36 (22%) as small, 21 (13%) as disproportionate, and 16 (10%) as not having microcephaly. 43 (26%) of the 164 infants had microcephaly at follow-up for an estimated prevalence of 5·9 per 1000 livebirths. We enrolled 114 control infants matched to the 43 infants classified as having microcephaly at follow-up. Infants with microcephaly at follow-up were more likely than control infants to be younger (OR 0·5, 95% CI 0·4–0·7), have recent Zika virus infection (21·9, 7·0–109·3), or a mother with Zika-like symptoms in the first trimester (6·2, 2·8–15·4). Once Zika virus infection and infant age were controlled for, we found no significant association between microcephaly and maternal demographics, medications, toxins, or other infections. Based on the presence of Zika virus antibodies in infants, we concluded that 35–87% of microcephaly occurring during the time of our investigation in northeast Brazil was attributable to Zika virus. We estimate 2–5 infants per 1000 livebirths in Paraíba had microcephaly attributable to Zika virus.
INTERPRETATION: Time of exposure to Zika virus and evidence of infection in the infants were the only risk factors associated with microcephaly. This investigation has improved understanding of the outbreak of microcephaly in northeast Brazil and highlights the need to obtain multiple measurements after birth to establish if an infant has microcephaly and the need for further research to optimize testing criteria for congenital Zika virus infection.

DOI: 10.1016/S2352-4642(18)30020-8
IMPACT FACTOR: N/A
CITED HALF-LIFE: N/A

START COMMENTARY: This study sought to quantify the prevalence of microcephaly in Paraiba, Brazil and the proportion of cases attributable to Zika virus; an important research gap during the epidemic. In addition, this study uncovered some challenges with the case definition used for microcephaly surveillance, as some of the identified cases did not actually have the condition when measured 1-7 months after birth. The number of cases was smaller than expected and this underpowered the analysis

examining effect modification. A limitation of this study was that the blood samples used to test for Zika virus were collected at the follow up visit rather than at the time of birth. Any infant with a positive IgM test for Zika was assumed to be infected in utero. This assumption could have led to misclassification as a positive test could reflect postnatal infection.

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4. Similarities and differences in child development from birth to age 3 years by sex and across four countries: a cross-sectional, observational study
   Ertem IO, Krishnamurthy V, Mulaudzi MC, Sguassero Y, Balta H, Gulumser O, et al.
   *Lancet Glob Health.*6(3). 2018 Mar.
   PubMed ID. 29433666

ABSTRACT
BACKGROUND: Knowledge about typical development is of fundamental importance for understanding and promoting child health and development. We aimed to ascertain when healthy children in four culturally and linguistically different countries attain developmental milestones and to identify similarities and differences across sexes and countries.
METHODS: In this cross-sectional, observational study, we recruited children aged 0–42 months and their caregivers between March 3, 2011, and May 18, 2015, at 22 health clinics in Argentina, India, South Africa, and Turkey. We obtained a healthy subsample, which excluded children with a low birthweight, perinatal complications, chronic illness, undernutrition, or anemia, and children with missing health data. Using the Guide for Monitoring Child Development, caregivers described their child's development in seven domains: expressive and receptive language, gross and fine motor, play, relating, and self-help. Clinicians examining the children also completed a checklist about the child's health status. We used logit and probit regression models based on the lowest deviance information criterion to generate Bayesian point estimates and 95% credible intervals for the 50th percentile ages of attainment of 106 milestones. We assessed the significance of differences between sexes and countries using predefined criteria and regions of practical equivalence.
FINDINGS: Of 10 246 children recruited, 4949 children (48·3%) were included in the healthy subsample. For the 106 milestones assessed, the median age of attainment was equivalent for 102 (96%) milestones across sexes and 81 (76%) milestones across the four countries. Across countries, median ages of attainment were equivalent for all play milestones, 20 (77%) of 26 expressive language milestones, ten (67%) of 15 receptive language milestones, nine (82%) of 11 fine motor milestones, 14 (88%) of 16 gross motor milestones, and eight (73%) of 11 relating milestones. However, across the four countries the median age of attainment was equivalent for only two (22%) of nine milestones in the self-help domain.
INTERPRETATION: The ages of attainment of developmental milestones in healthy children, and the similarities and differences across sexes and country samples might aid the development of international tools to guide policy, service delivery, and intervention research, particularly in low-income and middle-income countries.

DOI: 10.1016/S2214-109X(18)30003-2
IMPACT FACTOR: 17.7
CITED HALF-LIFE: 2.1

START COMMENTARY: This study uses cross-sectional data from healthy infants and children to compare the ages of milestone achievement by sex and country. This study is important for the field as it shows that most developmental milestones in early childhood are achieved at similar ages, between countries and genders. This supports the use of standardized instruments to assess development milestones, rather than tailoring instruments to a specific country context, which is time and resource intensive. In addition, the study provides estimates of age of attainment for more than 100 milestones across multiple domains. Results for each milestone are reported in Table 2 by gender and country. A limitation of this study is that the sample was identified through clinics and this may have lead to a

sampling bias for children who were less-well than the general population; however, the investigators applied exclusion criteria to identify a healthy sample of children.

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5. Effects of water quality, sanitation, handwashing, and nutritional interventions on diarrhoea and child growth in rural Bangladesh: a cluster randomised controlled trial
   Luby SP, Rahman M, Arnold BF, Unicomb L, Ashraf S, Winch PJ, et al.
   *Lancet Glob Health.*6(3). 2018 Mar.
   PubMed ID. 29396217

ABSTRACT
BACKGROUND: Diarrhea and growth faltering in early childhood are associated with subsequent adverse outcomes. We aimed to assess whether water quality, sanitation, and handwashing interventions alone or combined with nutrition interventions reduced diarrhea or growth faltering.
METHODS: The WASH Benefits Bangladesh cluster-randomized trial enrolled pregnant women from villages in rural Bangladesh and evaluated outcomes at 1-year and 2-years' follow-up. Pregnant women in geographically adjacent clusters were block-randomized to one of seven clusters: chlorinated drinking water (water); upgraded sanitation (sanitation); promotion of handwashing with soap (handwashing); combined water, sanitation, and handwashing; counselling on appropriate child nutrition plus lipid-based nutrient supplements (nutrition); combined water, sanitation, handwashing, and nutrition; and control (data collection only). Primary outcomes were caregiver-reported diarrhea in the past 7 days among children who were in utero or younger than 3 years at enrolment and length-for-age Z score among children born to enrolled pregnant women. Masking was not possible for data collection, but analyses were masked. Analysis was by intention to treat. This trial is registered at ClinicalTrials.gov, number NCC01590095.
FINGINGS: Between May 31, 2012, and July 7, 2013, 5551 pregnant women in 720 clusters were randomly allocated to one of seven groups. 1382 women were assigned to the control group; 698 to water; 696 to sanitation; 688 to handwashing; 702 to water, sanitation, and handwashing; 699 to nutrition; and 686 to water, sanitation, handwashing, and nutrition. 331 (6%) women were lost to follow-up. Data on diarrhea at year 1 or year 2 (combined) were available for 14 425 children (7331 in year 1, 7094 in year 2) and data on length-for-age Z score in year 2 were available for 4584 children (92% of living children were measured at year 2). All interventions had high adherence. Compared with a prevalence of 5·7% (200 of 3517 child weeks) in the control group, 7-day diarrhea prevalence was lower among index children and children under 3 years at enrolment who received sanitation (61 [3·5%] of 1760; prevalence ratio 0·61, 95% CI 0·46–0·81), handwashing (62 [3·5%] of 1795; 0·60, 0·45–0·80), combined water, sanitation, and handwashing (74 [3·9%] of 1902; 0·69, 0·53–0·90), nutrition (62 [3·5%] of 1766; 0·64, 0·49–0·85), and combined water, sanitation, handwashing, and nutrition (66 [3·5%] of 1861; 0·62, 0·47–0·81); diarrhea prevalence was not significantly lower in children receiving water treatment (90 [4·9%] of 1824; 0·89, 0·70–1·13). Compared with control (mean length-for-age Z score –1·79), children were taller by year 2 in the nutrition group (mean difference 0·25 [95% CI 0·15–0·36]) and in the combined water, sanitation, handwashing, and nutrition group (0·13 [0·02–0·24]). The individual water, sanitation, and handwashing groups, and combined water, sanitation, and handwashing group had no effect on linear growth.
INTERPRETATION: Nutrient supplementation and counselling modestly improved linear growth, but there was no benefit to the integration of water, sanitation, and handwashing with nutrition. Adherence was high in all groups and diarrhea prevalence was reduced in all intervention groups except water treatment. Combined water, sanitation, and handwashing interventions provided no additive benefit over single interventions.

DOI: 10.1016/S2214-109X(17)30490-4
IMPACT FACTOR: 17.7
CITED HALF-LIFE: 2.1

START COMMENTARY: There is little evidence on interventions that successfully improve growth and reduce diarrhea and there is little evidence comparing interventions that target a single vs multiple pathways of enteric pathogen transmission. This trial found that drinking water quality, sanitation, and handwashing interventions were not associated with improved linear growth trajectories, and that adding WASH to a nutritional intervention did not improve diarrheal or growth outcomes. These findings indicate that focusing resources on a single intervention that can be rolled out to a larger population may have a bigger impact on growth than a more complex intervention rolled out to a smaller population. Limitations of the study included a prevalence of diarrhea that was lower than anticipated in their sample size calculations, and likely misclassification of diarrhea by caregiver report, limiting statistical power for this outcome.

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6. Effect of a mass radio campaign on family behaviours and child survival in Burkina Faso: a repeated cross-sectional, cluster-randomised trial
   Sarrassat S, Meda N, Badolo H, Ouedraogo M, Some H, Bambara R, et al.
   *Lancet Glob Health.*6(3). 2018 Mar.
   PubMed ID. 29433668

ABSTRACT
BACKGROUND: Media campaigns can potentially reach a large audience at relatively low cost but, to our knowledge, no randomized controlled trials have assessed their effect on a health outcome in a low-income country. We aimed to assess the effect of a radio campaign addressing family behaviors on all-cause post-neonatal under-5 child mortality in rural Burkina Faso.
METHODS: In this repeated cross-sectional, cluster randomized trial, clusters (distinct geographical areas in rural Burkina Faso with at least 40 000 inhabitants) were selected by Development Media International based on their high radio listenership (>60% of women listening to the radio in the past week) and minimum distances between radio stations to exclude population-level contamination. Clusters were randomly allocated to receive the intervention (a comprehensive radio campaign) or control group (no radio media campaign). Household surveys were performed at baseline (from December, 2011, to February, 2012), midline (in November, 2013, and after 20 months of campaigning), and endline (from November, 2014, to March, 2015, after 32 months of campaigning). Primary analyses were done on an intention-to-treat basis, based on cluster-level summaries and adjusted for imbalances between groups at baseline. The primary outcome was all-cause post-neonatal under-5 child mortality. The trial was designed to detect a 20% reduction in the primary outcome with a power of 80%. Routine data from health facilities were also analyzed for evidence of changes in use and these data had high statistical power. The indicators measured were new antenatal care attendances, facility deliveries, and under-5 consultations. This trial is registered with ClinicalTrial. gov, number NCT01517230.
FINDINGS: The intervention ran from March, 2012, to January, 2015. 14 clusters were selected and randomly assigned to the intervention group (n=7) or the control group (n=7). The average number of villages included per cluster was 34 in the control group and 29 in the intervention group. 2269 (82%) of 2784 women in the intervention group reported recognizing the campaign's radio spots at endline. Post-neonatal under-5 child mortality decreased from 93·3 to 58·5 per 1000 livebirths in the control group and from 125·1 to 85·1 per 1000 livebirths in the intervention group. There was no evidence of an intervention effect (risk ratio 1·00, 95% CI 0·82–1·22; p>0·999). In the first year of the intervention, under-5 consultations increased from 68 681 to 83 022 in the control group and from 79 852 to 111 758 in the intervention group. The intervention effect using interrupted time-series analysis was 35% (95% CI 20–51; p<0·0001). New antenatal care attendances decreased from 13 129 to 12 997 in the control group and increased from 19 658 to 20 202 in the intervention group in the first year (intervention effect 6%, 95% CI 2–10; p=0·004). Deliveries in health facilities decreased from 10 598 to 10 533 in the control group and increased from 12 155 to 12 902 in the intervention group in the first year (intervention effect 7%, 95% CI 2–11; p=0·004).
INTERPRETATION: A comprehensive radio campaign had no detectable effect on child mortality. Substantial decreases in child mortality were observed in both groups over the intervention period, reducing our ability to detect an effect. This, nevertheless, represents the first randomized controlled trial to show that mass media alone can change health seeking behaviors.

DOI: 10.1016/S2214-109X(18)30004-4
IMPACT FACTOR: 17.7
CITED HALF-LIFE: 2.1

START COMMENTARY: Most previous studies on the effect of radio campaigns on health have not used a randomized design and when they did, had too few intended recipients of the intervention reporting exposure to determine an effect. To address this gap, this study randomizes clusters to intervention or control group and had an 82% reported exposure to the media campaign among intervention participants. For this study, the intervention included broadcasting on maternal health, newborn health, child nutrition, health care-seeking for childhood illnesses, bednets, and sanitation. Although there was no effect of the intervention on all-cause post-neonatal under-5 mortality or all-cause under-5 mortality, the authors did detect increases in the intervention group for the following intermediate outcomes: antenatal attendance, institutional deliveries, and under-5 consultations, suggesting benefit. A limitation of this study was the significant difference between control and intervention clusters, particularly for ethnicity, religion, wealth, distance to the nearest health facility, distance to the capitol (proxy for development), and facility delivery practices. The authors attempted to address these differences through controlling for a confounder score that was based on distance to the capitol, median distance to closest health facility, and facility delivery practices, and through controlling for differences in per-intervention mortality. Despite these efforts, there is likely unmeasured confounding. Another limitation is an estimated 20% of women in the control arm reported campaign recognition, indicating contamination of the control group.

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7. Early childhood growth and cognitive outcomes: Findings from the MAL-ED study
Scharf RJ, Rogawski ET, Murray-Kolb LE, Maphula A, Svensen E, Tofail F, et al.
Matern Child Nutr. 2018 Feb.
PubMed ID. 29392824

ABSTRACT
Although many studies around the world hope to measure or improve developmental progress in children to promote community flourishing and productivity, growth is sometimes used as a surrogate because cognitive skills are more difficult to measure. Our objective was to assess how childhood measures of anthropometry correlate with measures of child development in low income settings with high prevalence of poor nutrition and enteric disease, to inform studies considering growth outcomes in the absence of direct child developmental skill assessment. Children from the MAL-ED study were followed from birth to 24 months of age in field sites in 8 low- and middle-income countries across 3 continents. Monthly weight, length, and head circumference measurements were performed. At 24 months, the Bayley Scales of Infant and Toddler Development was administered. We correlated cognitive measures at 24 months with anthropometric measurements from birth to 2 years comparing 3 constructs: absolute attained monthly measures, summative difference in measures from the mean growth curve, and rate of change in measures. Growth faltering at multiple time periods is related to Bayley cognitive outcomes at 24 months. Birthweight, overall growth by 18–24 months, and rate of growth in the 6- to 18-month period were most associated with 24-month developmental scores. In this study, head circumference measurements, compared with length, was more closely linked to cognitive scores at 24 months. Notably, all studies between growth and cognitive outcomes exhibited low r2 values (0.001–0.049). Anthropometric measures, particularly head circumference, were related to cognitive development, although explaining a low percent of variance. When feasible, direct measures of child development may be more useful.

DOI: 10.1111/mcn.12584
IMPACT FACTOR: 2.5
CITED HALF-LIFE: 4.5

START COMMENTARY: This study examines how growth during the first 24 months of life is related to cognitive development, to determine whether simple measurements of child anthropometry can be utilized in lieu of developmental assessments that are expensive and complicated to administer. Data are from the MAL-ED study which studied children from 8 low and middle-income countries with high rates of enteric diseases and malnutrition. Figure 2 shows the associations between attained growth z scores by month with Bayley Cognitive Score at 24 months of age. While there is an association with some of these measures and cognitive development, it is likely other predictors drive the relationship more than these measures, such as maternal IQ. The authors excluded children who were born less than 1,500 g, had serious illness or extended hospital stays, multiple gestations, and whose mothers were less than 16 years old. A limitation of this study was that data were excluded from multiple study site locations because they was deemed to be of poor quality.

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8. Reagent Strips as an Aid to Diagnosis of Neonatal Meningitis in a Resource-limited Setting
   Burgoine K, Ikiror J, Naizuli K, Achom L, Akol S, Olupot-Olupot P, et al.
   J Trop Pediatr. 2018 Jan. [Epub ahead of print]
   PubMed ID. 29390160

ABSTRACT
BACKGROUND: Without early recognition and treatment, neonatal meningitis (NM) has a high mortality and morbidity. Although some neonates have features of NM, many do not. In many low-resource settings, the laboratory support to diagnose NM is not available, and bedside diagnostics are needed.
METHODS: This retrospective study was conducted in a neonatal unit in Uganda. Clear cerebrospinal fluid samples were routinely screened for glucose, protein and leukocytes on a Combur®-10 urinalysis reagent strip. A definitive diagnosis was made using laboratory analysis. The results of the screening and definitive tests were compared.
RESULTS: The reagent strip showed moderate sensitivity and high specificity for leukocytes ≥10×106 cells/l, high sensitivity for protein ≥100 mg/dl and high specificity for glucose <50 mg/dl.
CONCLUSION: The use of reagent strips has the potential to improve and hasten the diagnosis of probable NM in settings where adequate or timely laboratory support is not available.

DOI: 10.1093/tropej/fmy003
IMPACT FACTOR: 1.1
CITED HALF-LIFE: >10.0

START COMMENTARY: The gold standard for diagnosis of neonatal meningitis (NM) is to perform a lumbar puncture and conduct laboratory diagnostic tests on the sample. As many places in LMIC may not have access to these tests, timely lab results, or trained staff to perform them, a rapid point-of-care diagnostic for NM would greatly improve care. Urinalysis reagent strips have been found to be valid in older children and adults but it's validity for use in neonates has not been established. This study finds the reagent strips to be reasonably accurate for diagnosis of meningitis in neonates, with a sensitivity and specificity of 63.6 and 81.8, 94.1 and 79.0, and 6.3 and 100.0 for positive leucocytes, positive proteins, and negative glucose, respectively. The diagnostic accuracy of the reagent strip for detection of leukocytes, proteins, and glucose, compared to lab cerebrospinal fluid results, is presented in Table 1. Some limitations of this study are the small sample size and retrospective use of a convenience sample.

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9. Chitinase-3-like 1 is a biomarker of acute kidney injury and mortality in paediatric severe malaria
Conroy AL, Hawkes MT, Elphinstone R, Opoka RO, Namasopo S, Miller C, et al.
*Malar J.*17(1). 2018 Feb.
PubMed ID. 29448936

ABSTRACT
BACKGROUND: Chitinase-3-like 1 (CHI3L1) is a glycoprotein elevated in pediatric severe malaria, and an emerging urinary biomarker of acute kidney injury (AKI). Based on the hypothesis that elevated CHI3L1 levels in malaria are associated with disease severity, the relationship between plasma CHI3L1 levels, AKI and mortality was investigated in Ugandan children enrolled in a clinical trial evaluating inhaled nitric oxide (iNO) as an adjunctive therapy for severe malaria.
METHODS: Plasma CHI3L1 levels were measured daily for 4 days in children admitted to hospital with severe malaria and at day 14 follow up. AKI was defined using the Kidney Disease: Improving Global Outcomes consensus criteria. This is a secondary analysis of a randomized double-blind placebo-controlled trial of iNO versus placebo as an adjunctive therapy for severe malaria. Inclusion criteria were: age 1–10 years, and selected criteria for severe malaria. Exclusion criteria included suspected bacterial meningitis, known chronic illness including renal disease, haemoglobinopathy, or severe malnutrition. iNO was administered by non-rebreather mask for up to 72 h at 80 ppm.
RESULTS: CHI3L1 was elevated in patients with AKI and remained higher over hospitalization ($p < 0.0001$). Admission CHI3L1 levels were elevated in children who died. By multivariable analysis logCHI3L1 levels were associated with increased risk of in-hospital death (relative risk, 95% CI 4.10, 1.32–12.75, $p = 0.015$) and all-cause 6 month mortality (3.21, 1.47–6.98, $p = 0.003$) following correction for iNO and AKI. Treatment with iNO was associated with delayed CHI3L1 recovery with a daily decline of 34% in the placebo group versus 29% in the iNO group ($p = 0.012$). CHI3L1 levels correlated with markers of inflammation (CRP, sTREM-1, CXCL10), endothelial activation (Ang-2, sICAM-1) and intravascular haemolysis (LDH, haem, haemopexin).
CONCLUSION: CHI3L1 is a novel biomarker of malaria-associated AKI and an independent risk factor for mortality that is associated with well-established pathways of severe malaria pathogenesis including inflammation, endothelial activation, and haemolysis.

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CITED HALF-LIFE: 4.7

START COMMENTARY: AKI is now recognized as a common complication of malaria in children. This study investigates the use of CHI3L1 as a biomarker for AKI complications. Children with the highest levels of CHI3L1 were found to be more likely to have AKI, were more likely to have AKI at a higher stage, were more likely to die in the hospital or within 6 months, compared to children with the 3 lower levels of CHI3L1. As CHI3L1 was a predictor of death, independently from AKI, it is also possible that CHI3L1 is not just a biomarker for kidney health but may have more widespread application. After leaving the hospital but before 6 months, 16 children were lost to follow-up and 19 children reached 5 years of age (and were no longer followed, according to study protocol). The authors ran a sensitivity analysis (Table 3) to test different scenarios for the mortality of these children. All of these models still indicate an increased, significant relative risk in 6 month mortality with elevated CHI3L1, independent of the treatment arm in the original study. Previous literature has shown that iNO treatment is associated with an increased risk of AKI. The results linking iNO treatment to increased levels of CHI3L1 have been mixed. This study reports that once admitted to the hospital, those receiving iNO had a slower decline in CHI3L1 concentration than those not receiving iNO. {Return to List of Articles}

10. Infant and child mortality in relation to malaria transmission in KEMRI/CDC HDSS, Western Kenya: validation of verbal autopsy
Amek NO, Van Eijk A, Lindblade KA, Hamel M, Bayoh N, Gimnig J, et al.
*Malar J.*17(1). 2018 Jan.
PubMed ID. 29347942

ABSTRACT
BACKGROUND: Malaria transmission reduction is a goal of many malaria control programs. Little is known of how much mortality can be reduced by specific reductions in transmission. Verbal autopsy (VA) is widely used for estimating malaria specific mortality rates, but does not reliably distinguish malaria from other febrile illnesses. Overall malaria attributable mortality includes both direct and indirect deaths. It is unclear what proportion of the deaths averted by reducing malaria transmission are classified as malaria in VA.
METHODS: Both all-cause, and cause-specific mortality reported by VA for children under 5 years of age, were assembled from the KEMRI/CDC health and demographic surveillance system in Siaya county, rural Western Kenya for the years 2002–2004. These were linked to household-specific estimates of the *Plasmodium falciparum* entomological inoculation rate (EIR) based on high resolution spatio-temporal geostatistical modelling of entomological data. All cause and malaria specific mortality (by VA), were analysed in relation to EIR, insecticide-treated net use (ITN), socioeconomic status (SES) and parameters describing space–time correlation. Time at risk for each child was analyzed using Bayesian geostatistical Cox proportional hazard models, with time-dependent covariates. The outputs were used to estimate the diagnostic performance of VA in measuring mortality that can be attributed to malaria exposure.
RESULTS: The overall under-five mortality rate was 80 per 1000 person-years during the study period. Eighty-one percent of the total deaths were assigned causes of death by VA, with malaria assigned as the main cause of death except in the neonatal period. Although no trend was observed in malaria-specific mortality assessed by VA, ITN use was associated with reduced all-cause mortality in infants (hazard ratio 0.15, 95% CI 0.02, 0.63) and the EIR was strongly associated with both all-cause and malaria-specific mortality. 48.2% of the deaths could be attributed to malaria by analyzing the exposure–response relationship, though only 20.5% of VAs assigned malaria as the cause and the sensitivity of VAs was estimated to be only 26%. Although VAs assigned some deaths to malaria even in areas where there was estimated to be no exposure, the specificity of the VAs was estimated to be 85%.
CONCLUSION: Interventions that reduce *P. falciparum* transmission intensity will not only significantly reduce malaria diagnosed mortality, but also mortality assigned to other causes in under-5 year old children in endemic areas. In this setting, the VA tool based on clinician review substantially underestimates the number of deaths that could be averted by reducing malaria exposure in childhood, but has a reasonably high specificity. This suggests that malaria transmission-reducing interventions such as ITNs can potentially reduce overall child mortality by as much as twice the total direct malaria burden estimated from VAs.

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IMPACT FACTOR: 2.7
CITED HALF-LIFE: 4.7

START COMMENTARY: This study modeled the expected mortality rate due to malaria, based on the malaria transmission intensity-mortality relationship, and compared these results to VA-assessed cause of death. As there is no gold standard to validate malaria deaths using VA, it was unknown how accurate

VA was in identifying malaria as the cause of death in Siaya, Kenya. Table 4 presents the malaria VA results and malaria transmission intensity-mortality relationship showing that VA is very insensitive but has high specificity. In addition, authors model the excess mortality (without ITN data) due to malaria exposure in Figure 4 A-C. The malaria transmission intensity data is based upon analyses of mosquitos trapped at households and tested for the presence of circumsporozoite antigens.

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