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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

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OPTIMIZING BIRTH OUTCOMES FOR MOTHERS AND NEWBORNS

1. **Odon device for instrumental vaginal deliveries: results of a medical device pilot clinical study**
   Schvartzman JA, Krupitzki H, Merialdi M, Betrán AP, Requejo J, Nguyen MH, et al.
   *Reprod Health.*15(1). 2018 March.
   PubMed ID. 29526165

ABSTRACT
BACKGROUND: A prolonged and complicated second stage of labor is associated with serious perinatal complications. The Odon device is an innovation intended to perform instrumental vaginal delivery presently under development. We present an evaluation of the feasibility and safety of delivery with early prototypes of this device from an early terminated clinical study.
METHODS: Hospital-based, multi-phased, open-label, pilot clinical study with no control group in tertiary hospitals in Argentina and South Africa. Multiparous and nulliparous women, with uncomplicated singleton pregnancies, were enrolled during the third trimester of pregnancy. Delivery with Odon device was attempted under non-emergency conditions during the second stage of labor. The feasibility outcome was delivery with the Odon device defined as successful expulsion of the fetal head after one-time application of the device.
RESULTS: Of the 49 women enrolled, the Odon device was inserted successfully in 46 (93%), and successful Odon device delivery as defined above was achieved in 35 (71%) women. Vaginal, first and second degree perineal tears occurred in 29 (59%) women. Four women had cervical tears. No third or fourth degree perineal tears were observed. All neonates were born alive and vigorous. No adverse maternal or infant outcomes were observed at 6-weeks follow-up for all dyads, and at 1 year for the first 30 dyads.
CONCLUSIONS: Delivery using the Odon device is feasible. Observed genital tears could be due to the device or the process of delivery and assessment bias. Evaluating the effectiveness and safety of the further developed prototype of the BD Odon Device™ will require a randomized-controlled trial.

DOI: 10.1186/s12978-018-0485-8
IMPACT FACTOR: 2.2
CITED HALF-LIFE: 3.5

START COMMENTARY: This study seeks to evaluate the feasibility and safety of the Odon device, a new medical instrument intended to assist with vaginal births when there is prolonged second stage labor or complications. Currently, the options for instrumental vaginal deliveries are forceps or vacuum extractor, both of which present well-characterized risks to the infant and/or mother, have high failure rates, and are underutilized in low-resource settings. The Odon device, described in Figures 1 & 2, is intended to improve safety outcomes and increase capacity of lower-level medical staff to conducted instrument-assisted deliveries. During the conduct of this study, the device was licensed by Becton Dickinson and underwent several prototype revisions; the study was stopped early when the company decided to move forward with a randomized trial in the intended population. Fifty-nine percent of participants experienced a vaginal or perineal tear, but as there is no comparison group for the study participants, and the study was conducted in uncomplicated deliveries, investigators cannot determine if this incidence is above what would be expected. More concerning was the high rate of cervical tears (8.2%), however the investigators note that systematic assessment of the cervix following delivery could

lead to observation bias, in contrast to standard care settings where these would go unnoticed. While this study shows that using the Odon device is feasible for non-emergency deliveries, it is still unknown how well it will work in the intended population. Modification of the device prototype occurred throughout the study, and was noted to lead to improvements in success rates, however the group sizes were small.

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2. **Intermittent Preventive Therapy in Pregnancy and Incidence of Low Birth Weight in Malaria-Endemic Countries**
   Cates JE, Westreich D, Unger HW, Bauserman M, Adair L, Cole SR, et al.
   *Am J Public Health.*108(3). 2018 March.
   PubMed ID. 29346002

ABSTRACT
OBJECTIVES: To estimate the impact of hypothetical antimalarial and nutritional interventions (which reduce the prevalence of low midupper arm circumference [MUAC]) on the incidence of low birth weight (LBW).
METHODS: We analyzed data from 14 633 pregnancies from 13 studies conducted across Africa and the Western Pacific from 1996 to 2015. We calculated population intervention effects for increasing intermittent preventive therapy in pregnancy (IPTp), full coverage with bed nets, reduction in malaria infection at delivery, and reductions in the prevalence of low MUAC.
RESULTS: We estimated that, compared with observed IPTp use, administering 3 or more doses of IPTp to all women would decrease the incidence of LBW from 9.9% to 6.9% (risk difference = 3.0%; 95% confidence interval = 1.7%, 4.0%). The intervention effects for eliminating malaria at delivery, increasing bed net ownership, and decreasing low MUAC prevalence were all modest.
CONCLUSION: Increasing IPTp uptake to at least 3 doses could decrease the incidence of LBW in malaria-endemic countries. The impact of IPTp on LBW was greater than the effect of prevention of malaria, consistent with a nonmalarial effect of IPTp, measurement error, or selection bias.

DOI: 10.2105/AJPH.2017.304251
IMPACT FACTOR: 3.9
CITED HALF-LIFE: 9.9

START COMMENTARY: Investigators modelled the hypothetical effect of malaria and nutrition interventions on LWB incidence using pooled data from 13 studies in the Maternal Malaria and Malnutrition Initiative (M3), which focused on the co-burden of malaria and malnutrition during pregnancy. Based on the simulations, the intervention that would yield the greatest risk difference (RD) in LBW incidence was increasing the IPTp uptake to at least 3 doses; treating 33 pregnant women with 3 or more IPTp doses results in 1 fewer infant born LWB. The estimated benefit of other modeled interventions (including increasing bednet coverage and elimination of malaria at delivery) was much lower. The simulation effect of IPTp was greater than the estimated effect of malaria eradication in pregnancy; the investigators were unsure about the reason for this result but speculated that IPTp may have other benefits, including elimination of other pathogens or a reduction in maternal inflammation that may also contribute to the reduction in LWB. This study had a few limitations, including poor, self-reported data on bednet use that did not differentiate between treated and untreated nets. Another limitation is that women who attend more antenatal care visits are also more likely to receive 3 or more doses of IPTp. This could lead to selection bias among study participants and bias the simulations.

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3. **Pregnancy Outcomes after ZIKV Infection in French Territories in the Americas**
   Hoen B, Schaub B, Funk AL, Ardillon V, Boullard M, Cabié A, et al.
   *N Engl J Med.*378(11). 2018 March.
   PubMed ID. 29539287

ABSTRACT
BACKGROUND: The risk of congenital neurologic defects related to Zika virus (ZIKV) infection has ranged from 6 to 42% in various reports. The aim of this study was to estimate this risk among pregnant women with symptomatic ZIKV infection in French territories in the Americas.
METHODS: From March 2016 through November 2016, we enrolled in this prospective cohort study pregnant women with symptomatic ZIKV infection that was confirmed by polymerasechain-reaction (PCR) assay. The analysis included all data collected up to April 27, 2017, the date of the last delivery in the cohort.
RESULTS: Among the 555 fetuses and infants in the 546 pregnancies included in the analysis, 28 (5.0%) were not carried to term or were stillborn, and 527 were born alive. Neurologic and ocular defects possibly associated with ZIKV infection were seen in 39 fetuses and infants (7.0%; 95% confidence interval, 5.0 to 9.5); of these, 10 were not carried to term because of termination of pregnancy for medical reasons, 1 was stillborn, and 28 were live-born. Microcephaly (defined as head circumference more than 2 SD below the mean for sex and gestational age) was detected in 32 fetuses and infants (5.8%), of whom 9 (1.6%) had severe microcephaly (more than 3 SD below the mean). Neurologic and ocular defects were more common when ZIKV infection occurred during the first trimester (24 of 189 fetuses and infants [12.7%]) than when it occurred during the second trimester (9 of 252 [3.6%]) or third trimester (6 of 114 [5.3%]) (P = 0.001).
CONCLUSIONS: Among pregnant women with symptomatic, PCR-confirmed ZIKV infection, birth defects possibly associated with ZIKV infection were present in 7% of fetuses and infants. Defects occurred more frequently in fetuses and infants whose mothers had been infected early in pregnancy. Longer-term follow-up of infants is required to assess any manifestations not detected at birth.

DOI: 10.1056/NEJMoa1709481
IMPACT FACTOR: 72.4
CITED HALF-LIFE: 8.3

START COMMENTARY: Investigators sought to determine the risk of birth defects and adverse birth outcomes among pregnant women with PCR-confirmed symptomatic Zika infection from French Guiana, Guadeloupe, and Martinique. Women were enrolled in the study if they met the following criteria: ongoing pregnancy at any gestational stage and clinical symptoms consistent with acute Zika virus infection. A larger number of enrolled women who did not have Zika RNA detected by RT-PCR (n=458) were excluded from further study, and it is unclear what proportion of these may have been Zika infected. The incidence of birth outcomes and congenital abnormalities by trimester of maternal Zika virus infection are presented in Table 4. The risk of birth defects was 12.7% if infected in the first trimester and 3.6% and 5.3% if infected in the second and third trimesters, confirming earlier findings that the risk of congenital disease is greatest as a result of first-trimester infection. The primary limitations of the study were exclusion of asymptomatic Zika-infected women, and women who were Zika-infected but had undetectable Zika RNA in blood or urine. However, the authors note that the incidence of birth defects in a US-based study did not differ based upon symptomatic/asymptomatic disease, and that presence of maternal viremia is not known to be related to the risk of fetal outcomes. While acknowledging these inclusion criteria may limit generalizability, this approach minimized

misclassification rates compared to a reliance on a serologic Zika diagnosis. Finally, congenital anomalies were determined through fetal ultrasonography and neonatal clinical examination at the time of birth, and it is possible that undetected developmental sequelae could emerge later in infancy or childhood.

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4. **Malaria in pregnancy alters l-arginine bioavailability and placental vascular development**
McDonald CR, Cahill LS, Gamble JR, Elphinstone R, Gazdzinski LM, Zhong KJY, et al.
*Sci Transl Med.*10(431). 2018 March.
PubMed ID. 29514999

ABSTRACT
Reducing adverse birth outcomes due to malaria in pregnancy (MIP) is a global health priority. However, there are few safe and effective interventions. l-Arginine is an essential amino acid in pregnancy and an immediate precursor in the biosynthesis of nitric oxide (NO), but there are limited data on the impact of MIP on NO biogenesis. We hypothesized that hypoarginemia contributes to the pathophysiology of MIP and that l-arginine supplementation would improve birth outcomes. In a prospective study of pregnant Malawian women, we show that MIP was associated with lower concentrations of l-arginine and higher concentrations of endogenous inhibitors of NO biosynthesis, asymmetric and symmetric dimethylarginine, which were associated with adverse birth outcomes. In a model of experimental MIP, l-arginine supplementation in dams improved birth outcomes (decreased stillbirth and increased birth weight) compared with controls. The mechanism of action was via normalized angiogenic pathways and enhanced placental vascular development, as visualized by placental microcomputerized tomography imaging. These data define a role for dysregulation of NO biosynthetic pathways in the pathogenesis of MIP and support the evaluation of interventions to enhance l-arginine bioavailability as strategies to improve birth outcomes.

DOI: 10.1126/scitranslmed.aan6007
IMPACT FACTOR: 16.8
CITED HALF-LIFE: 3.6

START COMMENTARY: Malaria during pregnancy can lead to poor outcomes and is a leading cause of maternal morbidity and poor pregnancy outcomes. The authors hypothesized that interventions to improve placental angiogenesis could improve infant outcomes; specifically, they focused on L-argenine and inhibitors of NO. For this article, authors first compare birth outcomes and levels of L-argenine and NO-biosynthesis inhibitors between Malawian pregnant women with and without a positive blood smear for malaria. The authors found lower L-argenine and higher levels of NO-biosynthesis inhibitors in women with malaria, and that these differences persisted throughout pregnancy. Maternal nutritional status was positively associated with MUAC and maternal hemoglobin. Next, they show data from an experimental MIP mouse model in which mouse dams with and without malaria were supplemented with L-argine or no supplement. While there was no benefit of supplementation in animals without malaria, dams with malaria who received L-argenine had lower rates of stillbirth and higher birth weight compared to unsupplemented dams. Imaging showed that malaria-infected dams receiving L-argenine had an increased total number of placental vessel segments compared to unsupplemented dams. While conclusions from the human MIP model cannot be equated directly to humans, these data support evaluation of this intervention in human trials.

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5. **Household-level factors associated with relapse following discharge from treatment for moderate acute malnutrition**
   Stobaugh HC, Rogers BL, Webb P, Rosenberg IH, Thakwalakwa C, Maleta KM, et al.
   Br J Nutr. 2018 March. [Epub ahead of print]
   PubMed ID. 29502542

ABSTRACT
Factors associated with relapse among children who are discharged after reaching a threshold denoted 'recovered' from moderate acute malnutrition (MAM) are not well understood. The aim of this study was to identify factors associated with sustained recovery, defined as maintaining a mid-upper-arm circumference ≥12·5 cm for 1 year after release from treatment. On the basis of an observational study design, we analyzed data from an in-depth household (HH) survey on a sub-sample of participants within a larger cluster randomized controlled trial (cRCT) that followed up children for 1 year after recovery from MAM. Out of 1497 children participating in the cRCT, a subset of 315 children participated in this sub-study. Accounting for other factors, HH with fitted lids on water storage containers (P =0·004) was a significant predictor of sustained recovery. In addition, sustained recovery was better among children whose caregivers were observed to have clean hands (P= 0·053) and in HH using an improved sanitation facility (P=0·083). By contrast, socio-economic status and infant and young child feeding practices at the time of discharge and HH food security throughout the follow-up period were not significant. Given these results, we hypothesize that improved water, sanitation and hygiene conditions in tandem with management of MAM through supplemental feeding programs have the possibility to decrease relapse following recovery from MAM. Furthermore, the absence of associations between relapse and nearly all HH-level factors indicates that the causal factors of relapse may be related mostly to the child's individual, underlying health and nutrition status.

DOI: 10.1017/S0007114518000363
IMPACT FACTOR: 3.7
CITED HALF-LIFE: 7.2

START COMMENTARY: The study was nested into a RCT conducted in five districts in southern Malawi. Children were followed for 12 months following discharge to assess relapse rates, and investigators administered a household survey to a subsample of families within a week of discharge. Survey items included socioeconomic indicators (SES); infant and young child feeding practices (IYCF); WASH indicators; and maternal preconceptions of MAM, the supplemental feeding program and relapse. Tables 4 and 5 present the comparison between cofactors for children with relapse vs sustained recovery, and the results of a logistic regression model, respectively. MUAC at discharge was associated with a 20% increased rate of sustained recovery, and living in a home where all water storage containers have lids was associated with a 79% increased rate of sustained recovery, while all other cofactors were not significantly associated with recovery. A very large number of cofactors were assessed, and the investigators did not account for multiple comparisons. Additional limitations for this study included the convenience sampling scheme, and a lack of variation in household and caregiver characteristics and practices, which may have limited the ability to detect associations.

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6. **Dose-response Relationship Between Donor Human Milk, Mother's Own Milk, Preterm Formula, and Neonatal Growth Outcomes**
   Brownell EA, Matson AP, Smith KC, Moore JE, Esposito PA, Lussier MM, et al.
   J Pediatr Gastroenterol Nutr. 2018 March. [Epub ahead of print]
   PubMed ID. 29543698

ABSTRACT
BACKGROUND: A dose-response relationship between proportions of donor human milk(DHM) intake and in-NICU growth rates, if any, remains poorly defined. Objective was to evaluate interrelationships between percentages of DHM, mother's own milk (MOM) and preterm formula(PF) intake and neonatal growth parameters at 36 weeks postmenstrual age (PMA) or NICU discharge.
METHODS: Infants eligible for this single-center retrospective study were inborn at ≤32 weeks gestation or ≤1,800 grams, stayed in the NICU for ≥7 days, and received enteral nutrition consisting of human milk fortified with Enfamil human milk fortifier acidified liquid. Study exposures were defined as 10% increments in the total volumetric proportions of infant diet provided as MOM, DHM or PF. Outcomes were growth parameters at 36 weeks PMA or NICU discharge. Multivariable linear regression modeled the adjusted additive effect of infant diet on individual growth parameters.
RESULTS: 314 infants records were eligible for analysis. Using MOM as reference, the adjusted mean growth velocity for weight significantly decreased by 0.17 g/kg/day for every 10% increase in DHM intake, but did not vary with PF intake. The adjusted mean change in weight Z score significantly decreased with increasing proportion of DHM intake but significantly improved with increasing PF intake. The adjusted mean head circumference velocity was significantly decreased by 0.01cm/week for every 10% increase in DHM intake, in reference to MOM, but did not vary with PF intake. Neither proportion of DHM nor PF intake was associated with length velocity
CONCLUSION: When DHM and MOM are fortified interchangeably, preterm infants receiving incremental amounts of DHM are at increased risk of postnatal growth restriction. The dose response relationship between DHM, MOM, and PF and long-term growth and neurodevelopmental outcomes warrants further research.

DOI: 10.1097/MPG.0000000000001959
IMPACT FACTOR: 2.8
CITED HALF-LIFE: 7.3

START COMMENTARY: This US study is the first to investigate the dose-response relationship between DHM, MOM, and PF, and subsequent growth through weight, length, and head circumference. Infants eligible for the study were born between 1 August 2011 and 31 July 2015, met inclusion criteria for donor human milk, were in the NICU at least 7 days, received at least a portion of human milk that was fortified. Table 4 shows the association between maternal-infant factors and the rate of change in WAZ, HAZ, and head circumference z-scores. Results from this study are consistent with previous reports demonstrating that the use of DHM is associated with slower growth compared to MOM and speculate that this is due to a number of factors including pasteurization of DHF, which alters the biochemical composition of milk, and differences in breast milk collected term vs preterm. The authors note that breast milk from women delivering preterm is higher in protein, fat and amino acids than that of women delivering term, and the majority of banked DHM is obtained from mothers of term infants. Participants were not randomized to feeding modality, so there is potential for confounding. Additional limitations are that data came from a single hospital, and the amount of fortification received each day was a potential confounder that was not collected.

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7. **Mapping child growth failure in Africa between 2000 and 2015**
   Osgood-Zimmerman A, Millear AI, Stubbs RW, Shields C, Pickering BV, Earl L, et al.
   *Nature.*555(7694). 2018 Feb.
   PubMed ID. 29493591

ABSTRACT
Insufficient growth during childhood is associated with poor health outcomes and an increased risk of death. Between 2000 and 2015, nearly all African countries demonstrated improvements for children under 5 years old for stunting, wasting, and underweight, the core components of child growth failure. Here we show that striking subnational heterogeneity in levels and trends of child growth remains. If current rates of progress are sustained, many areas of Africa will meet the World Health Organization Global Targets 2025 to improve maternal, infant and young child nutrition, but high levels of growth failure will persist across the Sahel. At these rates, much, if not all of the continent will fail to meet the Sustainable Development Goal target—to end malnutrition by 2030. Geospatial estimates of child growth failure provide a baseline for measuring progress as well as a precision public health platform to target interventions to those populations with the greatest need, in order to reduce health disparities and accelerate progress.

DOI: 10.1038/nature25760
IMPACT FACTOR: 40.1
CITED HALF-LIFE: >10.0

START COMMENTARY: Authors used household survey data including the Demographic and Health Surveys (DHS), Multiple Indicator Cluster Surveys (MICS), Living Standards Measurement Study and Core Welfare Indicators Questionnaire, as well as multiple country-specific health and nutrition suveys to collect child anthropometric data. Using these data, prevalence estimates for each indicator were modelled on a 5x5 km grid over 51 countries in Africa annually, from 2000-2015. Although almost all African countries saw a reduction in levels of stunting, wasting, and underweight children under 5, the rates of change observed at a national level obscure great district-level heterogeneity in prevalence as well as changes over time (Figures 1 and 2). Based on model estimates, most of the continent would need to accelerate their declines in stunting and wasting from 2000 to 2015 to achieve WHO GNT targets; but sub-national disparities will remain. This type of analysis is important as it can guide targeted interventions to populations with the greatest need, and data are available at the sub-national (district/county) level for most countries. Authors note that the accuracy of the modelling depends on the quality, volume, and fidelity of nationally-represented surveys. Limitations of this study are sampling bias that excludes deceased children (many of whom would be expected to be stunted, wasted, or underweight) and the lack of child-specific covariates. The authors note that modelling is underway to map the burden of low birth weight, childhood overweight, anemia in women of reproductive age, and exclusive breastfeeding in similarly high resolution.

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8. **Global disability-adjusted life-year estimates of long-term health burden and undernutrition attributable to diarrhoeal diseases in children younger than 5 years**
   Troeger C, Colombara DV, Rao PC, Khalil IA, Brown A, Brewer TG, et al.
   *Lancet Glob Health.*6(3). 2018 March.
   PubMed ID. 29433665

ABSTRACT
BACKGROUND: Diarrhea is a leading cause of death and illness globally among children younger than 5 years. Mortality and short-term morbidity cause substantial burden of disease but probably underestimate the true effect of diarrhea on population health. This underestimation is because diarrheal diseases can negatively affect early childhood growth, probably through enteric dysfunction and impaired uptake of macronutrients and micronutrients. We attempt to quantify the long-term sequelae associated with childhood growth impairment due to diarrhea.
METHODS: We used the Global Burden of Diseases, Injuries, and Risk Factors Study framework and leveraged existing estimates of diarrhea incidence, childhood undernutrition, and infectious disease burden to estimate the effect of diarrheal diseases on physical growth, including weight and height, and subsequent disease among children younger than 5 years. The burden of diarrhea was measured in disability-adjusted life-years (DALYs), a composite metric of mortality and morbidity. We hypothesized that diarrhea is negatively associated with three common markers of growth: weight-for-age, weight for-height, and height-for-age Z-scores. On the basis of these undernutrition exposures, we applied a counterfactual approach to quantify the relative risk of infectious disease (subsequent diarrhea, lower respiratory infection, and measles) and protein energy malnutrition morbidity and mortality per day of diarrhea and quantified the burden of diarrheal disease due to these outcomes caused by undernutrition.
FINGINGS: Diarrhea episodes are significantly associated with childhood growth faltering. We found that each day of diarrhea was associated with height-for-age Z-score (–0·0033 [95% CI –0·0024 to –0·0041]; $p=4{\cdot}43 \times 10^{-14}$), weight-for-age Z-score (–0·0077 [–0·0058 to –0·0097]; $p=3{\cdot}19 \times 10^{-15}$), and weight-for-height Z-score (–0·0096 [–0·0067 to –0·0125]; $p=7{\cdot}78 \times 10^{-11}$). After addition of the DALYs due to the long-term sequelae as a consequence of undernutrition, the burden of diarrheal diseases increased by 39·0% (95% uncertainty interval [UI] 33·0–46·6) and was responsible for 55 778 000 DALYs (95% UI 49 125 400–62 396 200) among children younger than 5 years in 2016. Among the 15 652 300 DALYs (95% UI 12 951 300–18 806 100) associated with undernutrition due to diarrheal episodes, more than 84·7% are due to increased risk of infectious disease, whereas the remaining 15·3% of long term DALYs are due to increased prevalence of protein energy malnutrition. The burden of diarrhea has decreased substantially since 1990, but progress has been greater in long-term (78·7% reduction [95% UI 69·3–85·5]) than in acute (70·4% reduction [95% UI 61·7–76·5]) DALYs.
INTERPRETATION: Diarrhea represents an even larger burden of disease than was estimated in the Global Burden of Disease Study. In order to adequately address the burden of its long-term sequelae, a renewed emphasis on controlling the risk of diarrhea incidence may be required. This renewed effort can help further prevent the potential lifelong cost on child health, growth, and overall potential.

DOI: 10.1016/S2214-109X(18)30045-7
IMPACT FACTOR: 17.7
CITED HALF-LIFE: 2.1

START COMMENTARY: While diarrhea is known to be a leading cause of morbidity and mortality, the authors note that its impact is greatly underestimated because it contributes to long-term enteric dysfunction that increases morbidity and mortality through other illnesses. This systematic review and

meta-analysis generated country-specific estimates of DALYs attributed to diarrhea through growth impairment. In addition to composite estimates, the authors provide country-specific estimates of acute DALYs (immediately resulting from diarrhea), long-term sequelae of DALYs (burden associated with growth impairment), total DALYs (sum of acute and long-term) and the % increase when taking into account long-term DALYs attributed to growth impairment. The range of these percentages varies greatly by geographic region and country, from <10% in the wealthiest countries to >100% in the poorest countries, which are visualized in the maps in Figure 1 which show a) total DALYs in 2016, and b) the relative increase in total DALYs when including long-term sequalae attributed to diarrhea. Figure 4 shows temporal trends in total diarrhea DALYs from 1990-2016 by geographic region; while all areas experienced significant declines, there was substantial heterogeneity in progress. In the discussion, the authors note that when accounting for the long-term sequalae of diarrhea, the global burden of diarrhea moves from the fifth-leading to the third-leading cause of DALYs (morbidity and mortality) in children under 5 years globally. Limitations of this study include assumptions of causality between diarrhea and growth failure, and difficulty in modelling the likely bi-directional relationships between diarrhea, growth failure, and illness.

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9. **Child Health Outcomes After Presumptive Infection Treatment in Pregnant Women: A Randomized Trial**
   Hallamaa L, Cheung YB, Maleta K, Luntamo M, Ashorn U, Gladstone M, et al.
   *Pediatrics.*141(3). 2018 Feb. [Epub ahead of print]
   PubMed ID. 29472491

ABSTRACT
BACKGROUND AND OBJECTIVES: We showed earlier that presumptive infection treatment in pregnancy reduced the prevalence of neonatal stunting in a rural low-income setting. In this article, we assess how these gains were sustained and reflected in childhood growth, development, and mortality.
METHODS: We enrolled 1320 pregnant Malawian women in a randomized trial and treated them for malaria and other infections with either 2 doses of sulfadoxine-pyrimethamine (SP) (control), monthly SP, or monthly sulfadoxine-pyrimethamine and 2 doses of azithromycin (AZI-SP). Child height or length and mortality were recorded at 1, 6, 12, 24, 36, 48, and 60 months and development at 60 months by using Griffith's Mental Development Scales.
RESULTS: Throughout follow-up, the mean child length was 0.4 to 0.7 cm higher ($P < .05$ at 1–12 months), the prevalence of stunting was 6 to 11 percentage points lower ($P < .05$ at 12–36 months), and the 5-year cumulative incidence of stunting was 13 percentage points lower (hazard ratio: 0.70, 95% confidence interval [CI]: 0.60 to 0.83, $P < .001$) in the AZI-SP group than in the control group. The mean developmental score was 3.8 points higher in the AZI-SP group than in the control group (95% CI: 1.1 to 6.4, $P = .005$). Total mortality during pregnancy and childhood was 15.3%, 15.1%, and 13.1% ($P = .60$) in the control, monthly SP, and AZI-SP groups, respectively. Post neonatal mortality (secondary outcome) was 5.5%, 3.3%, and 1.9%, respectively (risk ratio of AZI-SP versus control: 0.34, 95% CI: 0.15 to 0.76, $P = .008$).
CONCLUSIONS: Provision of AZI-SP rather than 2 doses of SP during pregnancy reduced the incidence of stunting in childhood. AZI-SP during pregnancy also had a positive effect on child development and may have reduced post neonatal mortality.

DOI: 10.1542/peds.2017-2459
IMPACT FACTOR: 5.7
CITED HALF-LIFE: 8.9

START COMMENTARY: This study followed up participants from the Lugnwena Antenatal Intervention Study (LAIS) RCT for 5 years to long-term child outcomes. Previous studies have shown the positive impact of IPTp on birth weight, but this is the first study to evaluate this intervention into childhood. The LAIS study had 3 arms, with a control group (2 doses of SP only, standard of care), and two intervention groups: monthly SP and AZI-SP (monthly SP and 2 doses of azithromycin), and found the incidence of preterm birth and stunting at 1 month after delivery to be 35%-40% lower in the AZI-SP arm compared to those in the control group (Luntamo, Am J Trop Med Hyg. 2010). Primary outcomes for this second study were child WAZ, HAZ and stunting at 6, 12, 24, 36, 48, and 60 months of age; the total developmental score at 5 years; and the total number of abortions, stillbirths, and child deaths combined. Outcomes were collected from: 99.7% for mortality endpoint, 71.5% for developmental endpoints, and 78.3% and 71.7% for 2 and 5 year growth endpoints. The mean difference in absolute length was slightly greater at 1 month (0.4-0.7 cm) in the AZI-SP group compared to control, and this was maintained throughout 5 years of follow-up, although the growth trajectories of the two groups (slopes) appear similar in Figure 2. While the cumulative incidence of stunting or death was 30% lower in

the AZI-SP group at 5 years, the authors do not appear to have adjusted for baseline length or preterm birth, so it is unclear how much of their risk is due to this group being born earlier, and slightly smaller. Absolute composite GMDS-ER score was slightly higher in the AZI-SP group compared to control, which was mostly due to higher Performance subscale score. As about 28% of participants did not have data at 5 years for growth or development outcomes, the investigators conducted a sensitivity analysis using multiple imputation for missing outcomes and found the outcomes to still be robust.

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10. **A Randomized Trial of High-Flow Oxygen Therapy in Infants with Bronchiolitis**
Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J, et al.
*N Engl J Med.*378(12). 2018 March.
PubMed ID. 29562151

ABSTRACT
BACKGROUND: High-flow oxygen therapy through a nasal cannula has been increasingly used in infants with bronchiolitis, despite limited high-quality evidence of its efficacy. The efficacy of high-flow oxygen therapy through a nasal cannula in settings other than intensive care units (ICUs) is unclear.
METHODS: In this multicenter, randomized, controlled trial, we assigned infants younger than 12 months of age who had bronchiolitis and a need for supplemental oxygen therapy to receive either high-flow oxygen therapy (high-flow group) or standard oxygen therapy (standard-therapy group). Infants in the standard-therapy group could receive rescue high-flow oxygen therapy if their condition met criteria for treatment failure. The primary outcome was escalation of care due to treatment failure (defined as meeting ≥3 of 4 clinical criteria: persistent tachycardia, tachypnea, hypoxemia, and medical review triggered by a hospital early-warning tool). Secondary outcomes included duration of hospital stay, duration of oxygen therapy, and rates of transfer to a tertiary hospital, ICU admission, intubation, and adverse events.
RESULTS: The analyses included 1472 patients. The percentage of infants receiving escalation of care was 12% (87 of 739 infants) in the high-flow group, as compared with 23% (167 of 733) in the standard-therapy group (risk difference, −11 percentage points; 95% confidence interval, −15 to −7; P<0.001). No significant differences were observed in the duration of hospital stay or the duration of oxygen therapy. In each group, one case of pneumothorax (<1% of infants) occurred. Among the 167 infants in the standard-therapy group who had treatment failure, 102 (61%) had a response to high-flow rescue therapy.
CONCLUSIONS: Among infants with bronchiolitis who were treated outside an ICU, those who received high-flow oxygen therapy had significantly lower rates of escalation of care due to treatment failure than those in the group that received standard oxygen therapy.

DOI: 10.1056/NEJMoa1714855
IMPACT FACTOR: 72.4
CITED HALF-LIFE: 8.3

START COMMENTARY: Authors hypothesized that early treatment with high-flow therapy for infants with bronchiolitis and hypoxemia would result in fewer infants having treatment failure and subsequent escalation of care. To test this, they used a sample of infants from emergency departments and general pediatric inpatient units in 17 hospitals in Australia and New Zealand. Infants were excluded if they were critically ill who needed respiratory support and IUC admissions immediately; infants with cyanotic heart disease, basal skull fracture, upper airway obstruction, or craniofacial malformation; and infants who received oxygen therapy at home. For the escalation of care outcome analysis, authors conducted the analysis based on infants that received escalated care and based on infants that should have received escalation of care based prespecified clinical criteria. The analysis yielded very similar results, as shown in Table 2. More infants who received high-flow oxygen therapy remained free from treatment failure compared to those who received standard oxygen therapy, as shown in Figure 2.

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