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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. **Maternal anemia during pregnancy and small for gestational age: a systematic review and meta-analysis.**
   Badfar G, Shohani M, Soleymani A, Azami M.
   J Matern Fetal Neonatal Med. 2018 Jan.
   PubMed ID. 29183181

ABSTRACT
OBJECTIVE: Anemia is a major public health and nutritional problem in the world. Studies have reported the relationship between anemia during pregnancy and small for gestational age (SGA). Therefore, the present systematic review and meta-analysis was conducted to determine the relationship between maternal anemia during pregnancy and SGA.
METHOD: This meta-analysis was conducted without time limit until April 2017 based on the PRISMA protocol. Several international databases including Cochrane, Scopus, Web of Science (ISI), Pubmed, Embase, and Google Scholar search engine were searched independently by two researchers. The keywords include: anemia, pregnant women, gestational age, and pregnancy. The relative risk (RR) and 95% confidence interval were estimated regarding to the significance of the I2 index based on the random effects model. Data were analyzed using Comprehensive Meta-Analysis Software version 2.
RESULTS: Ten studies with a sample size including 620 080 pregnant women entered the meta-analysis process. The overall relationship between maternal anemia during pregnancy and SGA was not significant (RR = 1.11 [95%CI: 0.99-1.24, p = .074]). The relationship between anemia during pregnancy and SGA based on pregnancy trimester showed that maternal anemia was significant in the first trimester, (RR = 1.11 [95%CI: 1-1.22, p = .044]), but this relationship was not significant in the second trimester (RR = 1.11 [95%CI: 0.85-1.18, p = .91]).
CONCLUSIONS: Maternal anemia in the first trimester of pregnancy can be considered as a risk factor for negative pregnancy outcomes (SGA).

DOI: 10.1080/14767058.2017.1411477
IMPACT FACTOR: 1.8
CITED HALF-LIFE: 4.5

START COMMENTARY: A meta-analysis of anemia during pregnancy found that anemia exposure during the first trimester of pregnancy resulted in an increased relative risk for SGA birth outcomes, compared to non-anemic women. Anemia affects a large percentage of women in LMIC, with estimates of about 16-62% of women in LMIC being anemic. The inclusion criteria for studies was investigating the relationship between anemia during pregnancy and pregnancy outcomes. The exclusion criteria were duplicate studies, non-relevance to the topic, not experiencing anemia during pregnancy, SGA not addressed in the outcomes, review articles, cytological studies, animal studies, case reports and interventions. As exposure during first trimester was the only in-utero maternal anemia exposure associated with SGA birth outcome, this may impact the timing of interventions as many women do not know they are pregnant until they are several weeks into their first trimester. Figure 3 presents the relationship between anemia and SGA, disaggregated by first and second trimester exposures. A limitation of this meta-analysis are that different definition of anemia were used in some of the studies.

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2. **Provision of medical supply kits to improve quality of antenatal care in Mozambique: a stepped-wedge cluster randomised trial.**
   Betrán AP, Bergel E, Griffin S, Melo A, Nguyen MH, Carbonell A, et al.
   *Lancet Glob Health.*6(1). 2018 Jan.
   PubMed ID. 29241615

ABSTRACT
BACKGROUND: High levels of maternal and newborn mortality and morbidity remain a daunting reality in many low-income countries. Several interventions delivered during antenatal care have been shown to improve maternal and newborn outcomes, but stockouts of medical supplies at point of care can prevent implementation of these services. We aimed to evaluate whether a supply chain strategy based on the provision of kits could improve quality of care.
METHODS: We did a pragmatic, stepped-wedge, cluster-randomized controlled trial at ten antenatal care clinics in Mozambique. Clinics were eligible if they were not already implementing the proposed antenatal care package; they served at least 200 new pregnant women per year; they had Maternal and Child Health (MCH) nurses; and they were willing to participate. All women attending antenatal care visits at the participating clinics were included in the trial. Participating clinics were randomly assigned to shift from control to intervention on prespecified start dates. The intervention involved four components (kits with medical supplies, a cupboard to store these supplies, a tracking sheet to monitor stocks, and a one-day training session). The primary outcomes were the proportion of women screened for anemia and proteinuria, and the proportion of women who received mebendazole in the first antenatal care visit. The intervention was delivered under routine care conditions, and analyses were done according to the intention-to-treat principle. This trial is registered with the Pan African Clinical Trial Registry, number PACTR201306000550192.
FINDINGS: Between March 2014, and January, 2016, 218 277 antenatal care visits were registered, with 68 598 first and 149 679 follow-up visits. We found significant improvements in all three primary outcomes. In first visits, 5519 (14·6%) of 37 826 women were screened for anemia in the control period, compared with 30 057 (97·7%) of 30 772 in the intervention period (adjusted odds ratio 832·40; 99% CI 666·81–1039·11; p<0·0001); 3739 (9·9%) of 37 826 women were screened for proteinuria in the control period, compared with 29 874 (97·1%) of 30 772 in the intervention period (1875·18; 1447·56–2429·11; p<0·0001); and 17 926 (51·4%) of 34 842 received mebendazole in the control period, compared with 24 960 (88·2%) of 28 294 in the intervention period (1·88; 1·70–2·09; p<0·0001). The effect was immediate and sustained over time, with negligible heterogeneity between sites.
INTERPRETATION: A supply chain strategy that resolves stockouts at point of care can result in a vast improvement in quality during antenatal care visits, when compared with the routine national process for procurement and distribution of supplies.

DOI: 10.1016/S2214-109X(17)30421-7
IMPACT FACTOR: 17.7
CITED HALF-LIFE: 2.1

START COMMENTARY: Delivery of supply kits to address supply-chain issues at point of care to improve quality of antenatal care has not been rigorously tested, and almost all previous evidence is from observational studies. A detailed list of all outcomes assessed is presented in appendix Table S5, and includes additional screening tests, immunizations, folic acid supplementation, and treatments based upon risk/disease status. The three primary outcomes were selected after baseline data was collected, as these were the three screenings or tests with the lowest delivery rate. Figure 2 shows the effect sizes for all the outcomes examined, in addition to anemia, proteinuria, and deworming, the intervention was

found to significantly increase provision of hypertension screening, malaria preventative treatment, and syphilis screening and treatment. Two strengths of this study are the robust design and large sample size. A limitation of the study is the inability to tease apart the effects of each component of the intervention package.

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3. **Red cell distribution width and its association with mortality in neonatal sepsis.**
   Martin SL, Desai S, Nanavati R, Colah RB, Ghosh K, Mukherjee MB.
   J Matern Fetal Neonatal Med. 2018 Jan. [Epub ahead of print]
   PubMed ID. 29310472

ABSTRACT
OBJECTIVE: Neonatal sepsis is a major cause of mortality in the developing countries. However, with current severity scores and laboratory parameters, predicting outcomes of neonatal sepsis is a serious challenge. Red cell distribution width (RDW) is a readily available pragmatic means to predict outcomes of various comorbidities in adults and children, without causing any additional blood loss. However, its utility in neonates remains unexplored. Hence, the objective of the present study was to evaluate the association of RDW with neonatal sepsis and its role as a predictive marker for mortality.
METHODS: This Prospective observational study was carried out in a Level IIIB NICU for a period of 3 years. It involved comparison of RDW values of septic neonates with those of controls (matched for gestational age and birth weight) with an equal allocation ratio. A total of 251 septic neonates along with 251 controls >28 weeks of gestational age were enrolled. The RDW was derived from complete blood count done within first 6 hours of life. After arranging the RDW (median; interquartile range (IQR)), the values were categorized as those above the 50th percentile i.e. ≥20% and those below the 50th percentile i.e. <20%. The cumulative survival rates of the above two groups were assessed using the Kaplan-Meier curve and the log rank test.
RESULTS: RDW levels were significantly higher among the neonatal sepsis cases (19.90%) as compared to the controls (18.90%) with a p value of < .001. RDW was significantly higher amongst the nonsurvivors than survivors (p < .003). Kaplan-Meier curve showed that septic neonates having RDW values ≥20% had significantly increased mortality (p < .02) with a hazard ratio of 0.5.
CONCLUSIONS: High RDW is associated with neonatal sepsis and is an independent outcome predictor for mortality associated with neonatal sepsis.

DOI: 10.1080/14767058.2017.1421932
IMPACT FACTOR: 1.8
CITED HALF-LIFE: 4.5

START COMMENTARY: In sepsis, the acute inflammatory response alters both erythropoiesis and RBC maturation; these in turn affect RDW measurements, and the authors hypothesized that rise in RDW may predict the severity of sepsis and risk of mortality. RDW measures variation in red blood cell size or volume and is part of a standard CBC and available at health centers that have automated analyzers. Note that 3668/4170 potential study participants were excluded due to maternal anemia, medications expected to influence the fetal hematopoietic system, and those with other conditions expected to influence RDW independent of sepsis; this is expected to greatly reduce generalizability of the results.
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4. **Does postnatal care have a role in improving newborn feeding? A study in 15 sub–Saharan African countries.**
   Khan SM, Speizer IS, Singh K, Angeles G, Twum–Danso NAY, Barker P
   *Journal of Global Health.*7(2). 2017 December.
   PubMed ID. N/A

ABSTRACT
BACKGROUND: Breastfeeding is known as a key intervention to improve newborn health and survival while prelacteal feeds (liquids other than breastmilk within 3 days of birth) represents a departure from optimal feeding practices. Recent programmatic guidelines from the WHO and UNICEF outline the need to improve newborn feeding and points to postnatal care (PNC) as a potential mechanism to do so. This study examines if PNC and type of PNC provider are associated with key newborn feeding practices: breastfeeding within 1 day and prelacteal feeds.
METHODS: We use data from the Demographic and Health Surveys for 15 sub–Saharan African countries to estimate 4 separate pooled, multilevel, logistic regression models to predict the newborn feeding outcomes.
FINDINGS: PNC is significantly associated with increased breastfeeding within 1day (OR = 1.35, P < 0.001) but is not associated with PLFs (OR = 1.04, P = 0.195). PNC provided by nurses, midwives and untrained health workers is also associated with higher odds of breastfeeding within 1 day of birth (OR = 1.39, P < 0.001, (OR = 1.95, P < 0.001) while PNC provided by untrained health workers is associated with increased odds of PLFs (OR = 1.20, P = 0.017).
CONCLUSIONS: PNC delivered through customary care may be an effective strategy to improve the breastfeeding within 1 day but not to discourage PLFs. Further analysis should be done to examine how these variables operate at the country level to produce finer programmatic insight.

DOI: 10.7189/jogh.07.020506
IMPACT FACTOR: 2.8
CITED HALF-LIFE: 3.1

START COMMENTARY: There is a lack of evidence on whether PNC is effective in promoting exclusive breastfeeding in contrast to PLF. To address this gap, this study examined the association between PNC within 1 day and breastfeeding within 1 day and PLF. The results of the multilevel logistic regression for breastfeeding within 1 day and PLF are presented in Table 3. While breastfeeding was significantly associated with PNC, PNC within 1 day was not significantly associated with PLF. These findings indicate that PNC providers need to not only support timely initiation of breastfeeding, but also dissuade mothers from PLF practices. A limitation of this study is the cross-sectional design as the data used is from DHS surveys.

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5. **Identification and management of Shigella infection in children with diarrhoea: a systematic review and meta-analysis.**
   Tickell KD, Brander RL, Atlas HE, Pernica JM, Walson JL, Pavlinac PB.
   *Lancet Glob Health.*5(12). 2017 Dec.
   PubMed ID. 29132613

ABSTRACT
BACKGROUND: Shigella infections are a leading cause of diarrheal death among children in low-income and middle-income countries. WHO guidelines reserve antibiotics for treating children with dysentery. Reliance on dysentery for identification and management of Shigella infection might miss an opportunity to reduce Shigella-associated morbidity and mortality. We aimed to systematically review and evaluate Shigella-associated and dysentery-associated mortality, the diagnostic value of dysentery for the identification of Shigella infection, and the efficacy of antibiotics for children with Shigella or dysentery, or both.
METHODS: We did three systematic reviews (for mortality, diagnostic value, and antibiotic treatment of Shigella and dysentery), and meta-analyses where appropriate, of studies in resource-limited settings. We searched MEDLINE, Embase, and LILACS database for studies published before Jan 1, 2017, in English, French, and Spanish. We included studies of human beings with diarrhea and accepted all study-specific definitions of dysentery. For the mortality and diagnostic value searches, we excluded studies that did not include an effect estimate or data necessary to calculate this estimate. The search for treatment included only randomized controlled trials that were done after Jan 1, 1980 and assessed antibiotics in children (aged <18 years) with dysentery or laboratory-confirmed Shigella. We extracted or calculated odds ratios (ORs) and 95% CIs for relative mortality and did random-effects meta-analysis to arrive at pooled ORs. We calculated 95% CIs assuming a binomial distribution and did random-effects meta-regression of log-transformed sensitivity and specificity estimates for diagnostic value. We assessed the heterogeneity of papers included in these meta-analyses using the I2 statistic and evaluated publication bias using funnel plots. This review is registered with PROSPERO (CRD42017063896).
FINDINGS: 3649 papers were identified and 60 studies were included for analyses: 13 for mortality, 27 for diagnostic value, and 20 for treatment. Shigella infection was associated with mortality (pooled OR 2·8, 95% CI 1·6-4·8; p=0·000) whereas dysentery was not associated with mortality (1·3, 0·7-2·3; p=0·37). Between 1977 and 2016, dysentery identified 1·9-85·9% of confirmed Shigella infections, with sensitivity decreasing over time (p=0·04). Ten (50%) of 20 included antibiotic trials were among children with dysentery, none were placebo-controlled, and two (10%) evaluated antibiotics no longer recommended for acute infectious diarrhea. Ciprofloxacin showed superior microbiological, but not clinical, effectiveness compared with pivmecillinam, and no superior microbiological and clinical effectiveness compared with gatifloxacin. Substantial heterogeneity was reported for meta-analyses of the Shigella-associated mortality studies (I2=78·3%) and dysentery-associated mortality studies (I2=73·2%). Too few mortality studies were identified to meaningfully test for publication bias. No evidence of publication bias was found in this analysis of studies of diagnostic value.
INTERPRETATION: Current WHO guidelines appear to manage dysentery effectively but might miss opportunities to reduce mortality among children infected with Shigella who present without bloody stool. Further studies should quantify potential decreases in mortality and morbidity associated with antibiotic therapy for children with non-dysenteric Shigella infection.

DOI: 10.1016/S2214-109X(17)30392-3.

IMPACT FACTOR: 17.7
CITED HALF-LIFE: 2.1

START COMMENTARY: Current WHO guidelines for use of antibiotics to treat diarrhea include detection of blood in the stool (dysentery), which is usually associated with *Shigella dysenteriae*. This study indicates that the current international guidelines may not address the full burden of Shigella-related mortality. Recently, there has been a shift in prevalence of Shigella species, with a decline in prevalence of *S. dysenteriae*. The meta-analysis shows a stronger association between mortality and Shigella than between mortality and dysentery (Figures 2 and 3), supporting the author's claim that the current guidelines need revised. Authors also evaluated the diagnostic value of dysentery for identifying cases of Shigella. Figure 4 shows the sensitivity of dysentery for the detection of Shigella infection decreasing over calendar time. A limitation of the study is under-representation of data from South America and Africa, which impacts the generalizability of findings.

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6. **Appropriateness of clinical severity classification of new WHO childhood pneumonia guidance: a multi-hospital, retrospective, cohort study**
   Agweyu A, Lilford RJ, English M; Clinical Information Network Author Group.
   *Lancet Glob Health.*6(1). 2018 Jan.
   PubMed ID. 29241618

ABSTRACT
BACKGROUND: Management of pneumonia in many low-income and middle-income countries is based on WHO guidelines that classify children according to clinical signs that define thresholds of risk. We aimed to establish whether some children categorized as eligible for outpatient treatment might have a risk of death warranting their treatment in hospital.
METHODS: We did a retrospective cohort study of children aged 2-59 months admitted to one of 14 hospitals in Kenya with pneumonia between March 1, 2014, and Feb 29, 2016, before revised WHO pneumonia guidelines were adopted in the country. We modelled associations with inpatient mortality using logistic regression and calculated absolute risks of mortality for presenting clinical features among children who would, as part of revised WHO pneumonia guidelines, be eligible for outpatient treatment (non-severe pneumonia).
FINDINGS: We assessed 16 162 children who were admitted to hospital in this period. 832 (5%) of 16 031 children died. Among groups defined according to new WHO guidelines, 321 (3%) of 11 788 patients with non-severe pneumonia died compared with 488 (14%) of 3434 patients with severe pneumonia. Three characteristics were strongly associated with death of children retrospectively classified as having non-severe pneumonia: severe pallor (adjusted risk ratio 5·9, 95% CI 5·1-6·8), mild to moderate pallor (3·4, 3·0-3·8), and weight-for-age Z score (WAZ) less than -3 SD (3·8, 3·4-4·3). Additional factors that were independently associated with death were: WAZ less than -2 to -3 SD, age younger than 12 months, lower chest wall indrawing, respiratory rate of 70 breaths per min or more, female sex, admission to hospital in a malaria endemic region, moderate dehydration, and an axillary temperature of 39°C or more.
INTERPRETATION: In settings of high mortality, WAZ less than -3 SD or any degree of pallor among children with non-severe pneumonia was associated with a clinically important risk of death. Our data suggest that admission to hospital should not be denied to children with these signs and we urge clinicians to consider these risk factors in addition to WHO criteria in their decision making.

DOI: 10.1016/S2214-109X(17)30448-5.
IMPACT FACTOR: 17.7
CITED HALF-LIFE: 2.1

START COMMENTARY: This retrospective cohort study assesses risk factors for death among children treated for pneumonia in district hospitals in Kenya. It is the largest published individual analysis of risk factors for mortality among children admitted to hospital for pneumonia. The study is also particularly important as its findings are from a high mortality setting with high prevalence of comorbidity, unlike most previous studies. Infants in Kenya are now receiving Hib and pneumococcal conjugate vaccines which is expected to decrease pneumonia burden, but this analysis was restricted to children born before the introduction of these vaccines. Authors report that 321 children classified as having non-severe pneumonia who would be considered suitable for outpatient care according to current guidelines nonetheless died. The risk factors for death among patients with non-severe pneumonia are presented in Figure 2. The authors note that in high mortality settings, WHO classifications of severity of pneumonia may be insufficient in determining mortality risk, and wasting and pallor should be considered as additional criteria for hospitalization. {Return to List of Articles}

7. **BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity.**
   Arts RJW, Moorlag SJCFM, Novakovic B, Li Y, Wang SY, Oosting M, et al.
   *Cell Host Microbe.*23(1). 2018 Jan.
   PubMed ID. 29324233

ABSTRACT
The tuberculosis vaccine bacillus Calmette-Guérin (BCG) has heterologous beneficial effects against non-related infections. The basis of these effects has been poorly explored in humans. In a randomized placebo-controlled human challenge study, we found that BCG vaccination induced genome-wide epigenetic reprograming of monocytes and protected against experimental infection with an attenuated yellow fever virus vaccine strain. Epigenetic reprogramming was accompanied by functional changes indicative of trained immunity. Reduction of viremia was highly correlated with the upregulation of IL-1β, a heterologous cytokine associated with the induction of trained immunity, but not with the specific IFNγ response. The importance of IL-1β for the induction of trained immunity was validated through genetic, epigenetic, and immunological studies. In conclusion, BCG induces epigenetic reprogramming in human monocytes in vivo, followed by functional reprogramming and protection against non-related viral infections, with a key role for IL-1β as a mediator of trained immunity responses.

DOI: 10.1016/j.chom.2017.12.010.
IMPACT FACTOR: 14.9
CITED HALF-LIFE: 4.3

START COMMENTARY: Although numerous epidemiologic studies suggest a protective benefit for BCG immunization in reducing mortality, respiratory tract infections, and neonatal sepsis independent of TB, the mechanisms for these broad protective effects are not well-understood. This study investigates a potential immunological basis for this protection, specifically, through “trained immunity” in the innate immune response. Trained immunity (or innate immune memory) is an emerging concept that challenges the dichotomous model of innate versus adaptive immunity. Trained immunity describes epigenetic changes to transcription programs in innate immune responses, which do not equate to development of pathogen-specific memory cells, but do broadly increase response effectiveness and decrease response time to subsequent infectious challenges (see Netea, Science 2016 for a recent review). The study found that BCG protection against yellow fever virus challenge was mediated by the modification of monocyte transcription profiles that correlated directly with the production of innate cytokines.

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8. **Inhaled nitric oxide and cognition in pediatric severe malaria: A randomized double-blind placebo controlled trial.**
   Bangirana P, Conroy AL, Opoka RO, Hawkes MT, Hermann L, Miller C, et al.
   *PLoS One.*13(1). 2018 Jan.
   PubMed ID. 29370261

ABSTRACT
BACKGROUND: Severe malaria is a leading cause of acquired neurodisability in Africa and is associated with reduced nitric oxide (NO) bioavailability. A neuroprotective role for inhaled NO has been reported in animal studies, and administration of inhaled NO in preterm neonates with respiratory distress syndrome is associated with a 47% reduced risk of cognitive impairment at two years of age.
METHODS: A randomized double-blind placebo-controlled trial of inhaled NO versus placebo as an adjunctive therapy for severe malaria was conducted in Uganda between 2011 and 2013. Children received study gas for a maximum 72 hours (inhaled NO, 80 parts per million; room air placebo). Neurocognitive testing was performed on children<5 years at 6 month follow-up. The neurocognitive outcomes assessed were overall cognition (a composite of fine motor, visual reception, receptive language, and expressive language), attention, associative memory, and the global executive composite. Main outcomes were attention, associative memory, and overall cognitive ability.
RESULTS: Sixty-one children receiving iNO and 59 children receiving placebo were evaluated. Forty-two children (35.0%) were impaired in at least one neurocognitive domain. By intention-to-treat analysis, there were no differences in unadjusted or unadjusted age-adjusted z-scores for overall cognition (β (95% CI): 0.26 (-0.19, 0.72), p = 0.260), attention (0.18 (-0.14, 0.51), p = 0.267), or memory (0.14 (-0.02, 0.30), p = 0.094) between groups by linear regression. Children receiving inhaled NO had a 64% reduced relative risk of fine motor impairment than children receiving placebo (relative risk, 95% CI: 0.36, 0.14-0.96) by log binomial regression following adjustment for anticonvulsant use.
CONCLUSIONS: Severe malaria is associated with high rates of neurocognitive impairment. Treatment with inhaled NO was associated with reduced risk of fine motor impairment. These results need to be prospectively validated in a larger study powered to assess cognitive outcomes in order to evaluate whether strategies to increase bioavailable NO are neuroprotective in children with severe malaria.

DOI: 10.1371/journal.pone.0191550.
IMPACT FACTOR: 2.8
CITED HALF-LIFE: 3.7

START COMMENTARY: This is the first randomized control trial investigating neurocognitive outcomes among children receiving iNO adjunctive therapy for severe malaria. The results of the 6 month follow up test show that treatment with iNO was associated with reduced RR of fine motor impairments, but this was the only significant outcome associated with iNO exposure. The study had good retention at follow up with 87% of iNO treated patients and 89% of placebo treated patients returning for cognitive testing 6 months after the intervention. The inclusion criteria were: children 1-10 years old with a positive three band malaria rapid diagnostic test, presence of symptoms of severe malaria, and willing and able to participate. Children with a baseline methemoglobinemia of greater than 2 percent, a history of chronic illness, and severe malnutrition were excluded from the study. A limitation of this study is that it was small and underpowered to detect a difference across multiple neurocognitive outcomes.

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9. **A diagnostic and epidemiologic investigation of acute febrile illness (AFI) in Kilombero, Tanzania.**
   Hercik C, Cosmas L, Mogeni OD, Wamola N, Kohi W, Omballa V, et al.
   *PLoS One.*12(12). 2017 Dec.
   PubMed ID. 29287070

ABSTRACT
INTRODUCTION: In low-resource settings, empiric case management of febrile illness is routine as a result of limited access to laboratory diagnostics. The use of comprehensive fever syndromic surveillance, with enhanced clinical microbiology, advanced diagnostics and more robust epidemiologic investigation, could enable healthcare providers to offer a differential diagnosis of fever syndrome and more appropriate care and treatment.
METHODS: We conducted a year-long exploratory study of fever syndrome among patients ≥ 1 year if age, presenting to clinical settings with an axillary temperature of ≥37.5°C and symptomatic onset of ≤5 days. Blood and naso-pharyngeal/oral-pharyngeal (NP/OP) specimens were collected and analyzed, respectively, using AFI and respiratory TaqMan Array Cards (TAC) for multi-pathogen detection of 57 potential causative agents. Furthermore, we examined numerous epidemiologic correlates of febrile illness, and conducted demographic, clinical, and behavioral domain-specific multivariate regression to statistically establish associations with agent detection.
RESULTS: From 15 September 2014-13 September 2015, 1007 febrile patients were enrolled, and 997 contributed an epidemiologic survey, including: 14% (n = 139) 1<5yrs, 19% (n = 186) 5-14yrs, and 67% (n = 672) ≥15yrs. AFI TAC and respiratory TAC were performed on 842 whole blood specimens and 385 NP/OP specimens, respectively. Of the 57 agents surveyed, Plasmodium was the most common agent detected. AFI TAC detected nucleic acid for one or more of seven microbial agents in 49% of AFI blood samples, including: Plasmodium (47%), Leptospira (3%), Bartonella (1%), Salmonella enterica (1%), Coxiella burnetii (1%), Rickettsia (1%), and West Nile virus (1%). Respiratory TAC detected nucleic acid for 24 different microbial agents, including 12 viruses and 12 bacteria. The most common agents detected among our surveyed population were: Haemophilus influenzae (67%), Streptococcus pneumoniae (55%), Moraxella catarrhalis (39%), Staphylococcus aureus (37%), Pseudomonas aeruginosa (36%), Human Rhinovirus (25%), influenza A (24%), Klebsiella pneumoniae (14%), Enterovirus (15%) and group A Streptococcus (12%). Our epidemiologic investigation demonstrated both age and symptomatic presentation to be associated with a number of detected agents, including, but not limited to, influenza A and Plasmodium. Linear regression of fully-adjusted mean cycle threshold (Ct) values for Plasmodium also identified statistically significant lower mean Ct values for older children (20.8), patients presenting with severe fever (21.1) and headache (21.5), as well as patients admitted for in-patient care and treatment (22.4).
CONCLUSIONS: This study is the first to employ two syndromic TaqMan Array Cards for the simultaneous survey of 57 different organisms to better characterize the type and prevalence of detected agents among febrile patients. Additionally, we provide an analysis of the association between adjusted mean Ct values for Plasmodium and key clinical and demographic variables, which may further inform clinical decision-making based upon intensity of infection, as observed across endemic settings of sub-Saharan Africa.

DOI: 10.1371/journal.pone.0189712.
IMPACT FACTOR: 2.8
CITED HALF-LIFE: 3.7

START COMMENTARY: This study assesses the burden of malaria and non-malaria agents in children with fever in Kilombero, Tanzania. To identify the type and prevalence of bloodstream and respiratory agents, investigators utilized highly sensitive multi-pathogen molecular diagnostics. Malaria was the most common agent detected with 12% of children 1<5 years old and 34% of children 5<14 years old testing positive. Table 3 presents the viral, bacterial, and parasitic agents detected, by age group. This table shows that *M. catarrhalis*, Adenovirus, Enterovirus, and RSV all decreased in prevalence with age. A limitation of this study is that all data came from one hospital and one clinic in an area highly endemic for malaria, limiting the generalizability of the findings. It was also not possible to attribute an etiologic relationship between an infection and fever in children with multiple pathogens identified.

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10. **A novel risk classification system for 30-day mortality in children undergoing surgery.**
Akbilgic O, Langham MR Jr., Walter AI, Jones TL, Huang EY, Davis RL.
*PLoS One.*13(1). 2018 Jan.
PubMed ID. 29351327

ABSTRACT
A simple, objective and accurate way of grouping children undergoing surgery into clinically relevant risk groups is needed. The purpose of this study, is to develop and validate a preoperative risk classification system for postsurgical 30-day mortality for children undergoing a wide variety of operations. The National Surgical Quality Improvement Project-Pediatric participant use file data for calendar years 2012-2014 was analyzed to determine preoperative variables most associated with death within 30 days of operation (D30). Risk groups were created using classification tree analysis based on these preoperative variables. The resulting risk groups were validated using 2015 data, and applied to neonates and higher risk CPT codes to determine validity in high-risk subpopulations. A five-level risk classification was found to be most accurate. The preoperative need for ventilation, oxygen support, inotropic support, sepsis, the need for emergent surgery and a do not resuscitate order defined non-overlapping groups with observed rates of D30 that vary from 0.075% (Very Low Risk) to 38.6% (Very High Risk). When CPT codes where death was never observed are eliminated or when the system is applied to neonates, the groupings remained predictive of death in an ordinal manner.

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START COMMENTARY: This study aims to develop a simple system for mortality risk stratification in children undergoing surgery, as there are limitations with the current risk stratification systems. Table 4 presents the 5 risk stratified groups with their criteria and risk of mortality within 30 days. The groups are based off 6 directly observed clinical variables, making this system simple and objective. The variables are if the patient: is on a ventilator, has oxygen support, has a do not resuscitate order, has sepsis, has inotropic support, and is an emergent case. Data for this study is from the American College of Surgeons National Surgical Quality Improvement Project-Pediatric Participant Use Files for 2012 through 2015. A strength of this study was the large and complete dataset used to create the risk stratified groups. A limitation is that the study is set in the US, which impacts the generalizability of results.

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