Addressing adverse outcomes following acute illness among children in Sub-Saharan Africa: predicting risks and cost-effectiveness

Rebecca Brander

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Reading Committee:
Judd Walson, Chair
Marcia Weaver
Patricia Pavlinac

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Abstract

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Rebecca Brander

Chair of the supervisory committee:
Judd Walson
Departments of Global Health, Epidemiology, Pediatrics

Children under age 5 in sub-Saharan Africa suffer a disproportionately high burden of infections disease, and the consequences of these conditions extend beyond the period during which the child is acutely ill. Children remain at high risk of mortality in the time period following a severe infectious disease, and, in the case of diarrhea, linear growth faltering. Interventions are needed to address these adverse outcomes following acute illness, but little is known about which children are at high risk, whether antibiotics may be effective, or the relative cost-effectiveness of various antibiotic administration strategies. We identified risk and predictive factors of linear growth faltering following moderate-to-severe diarrheal disease, and evaluated whether children who were exposed to antibiotics at diarrhea presentation had lower risks of linear growth faltering than children who were unexposed. Further, we compared two methods for collected patient-level hospitalization cost data and evaluated the comparative cost-effectiveness of mass distribution of azithromycin vs targeted azithromycin strategies. Using data from the Global Enteric Multicenter Study of children 0-59 moths old in 7 low- and middle-income countries in Africa and Asia presenting with moderate-to-severe diarrhea, we used linear regression to identify clinical and sociodemographic factors associated with loss in length-for-age z-score (LAZ) in the 50-90 days following presentation with moderate-to-severe diarrhea, and poisson regression with robust standard errors to identify factors associated with severe linear growth faltering (loss of ≥ 0.5 LAZ in the study period). Young age, nutritional status (low weight-for-length z-score, or high length-for-age z-score at presentation), high socioeconomic status, and severity of disease (hospitalization, presentation with fever, comorbidities, or general danger signs) identified children at high risk of linear growth faltering. These populations may benefit from diarrhea management interventions address post-diarrhea linear growth faltering. To evaluate the effects of antibiotics during moderate-to-severe diarrhea on linear growth, we used linear regression to estimate associations between antibiotic exposure (any antibiotic given or prescribed at diarrhea presentation) and linear growth faltering, using propensity score adjustment for factors associated with likelihood of receiving antibiotics. After propensity score adjustment, children who received antibiotics lost 0.04 less LAZ than those who did not (95% confidence interval: 0.01, 0.07) and were 20% less likely to experience severe linear growth faltering (adjusted odds ratio: 0.80 [0.69, 0.94]). Antibiotic management may offer modest protection against linear growth faltering in a sub-set of high risk children, but clinical trial evidence will be needed and the benefits should be weighed against the consequences. To evaluate the completeness of medical record documentation for the purposes of costing, we collected resource utilization data on children 1-

59 months old hospitalized in a public hospital in western Kenya two different ways: by direct observation and medical record abstraction. Only 38% of children had medical records that completely documented all resources that were received. Micro-costing by medical record abstraction may slightly underestimate costs, but researchers should select the data collection method that best fits the goals and budget of the project Finally, we constructed a decision tree model to estimate the cost-effectiveness of several azithromycin strategies for preventing mortality: mass drug administration (MDA) of azithromycin to children 1-59 months old, MDA to children 1-5 months old, and azithromycin administered at hospital discharge to children recently hospitalized for any infectious condition. MDA to children 1-59 months old would cost approximately $14/disability-adjusted-life-year (DALY) averted, MDA to children 1-5 months old would cost approximately $5/DALY averted, and post-discharge azithromycin would cost approximately $3/DALY averted. All azithromycin strategies would be highly cost-effective for preventing mortality, but targeting azithromycin to a high mortality population would be even more cost-effective.

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INTRODUCTION

The burden of infectious disease is disproportionately high in children under age five in Sub-Saharan Africa (SSA),[1–3] and the consequences of disease extend beyond the period of acute illness. Children who were recently hospitalized experience a mortality rate in the months following hospital discharge that is 6 to 8 times higher than children who were not hospitalized, and are at high risk for being re-hospitalized as well.[4–6] In addition, many of these children experience linear growth deficits following acute illness.[7–9] Linear growth faltering, if left unaddressed, can lead to irreversible stunting, an indicator of chronic malnutrition that is associated with substantial health and developmental consequences, including mortality.[10,11] In order to accelerate progress toward the Sustainable Development Goals target of reducing under-5 mortality,[12,13] interventions are urgently needed to address linear growth faltering and mortality that occur in the period following acute illness in SSA.

Antibiotics may be an effective and affordable intervention to improve these long-term outcomes. The majority of child deaths in SSA are attributed to infectious causes[2] and antibiotics are key interventions for the treatment or prevention of many bacterial infectious diseases. Antibiotics also have growth-promoting effects in low-resource settings.[14] While antibiotics are ideally reserved for when there is a confirmed diagnosis of a bacterial infection, such confirmation is not available in many low resource settings such as SSA due to access and affordability and thus antibiotics are used empirically. Empiric antibiotic use may be targeted to groups of children known to be at high risk of bacterial infections, such as children with HIV or severe acute malnutiriont. Mass drug administration (MDA) of antibiotics, including AZM, are also being considered for implementation in high child mortality regions of SSA following clinical trial evidence of mortality reduction with this strategy. Mass distribution, however, can lead to widespread antibiotic resistance[15] and may be less cost-effective than administration targeting high-risk groups.[16] Antibiotic administration targeting children at high risk of post-acute illness growth faltering and mortality may be an antibiotic sparing, highly cost-effective strategy to improving these outcomes.

In order to develop targeted antibiotic interventions, there is a need to understand which children realize greatest benefit from empiric antibiotic administration. Children with a recent episode of moderate-to-severe diarrhea (MSD) represent an ideal sub-population to evaluate questions around targeting antibiotics. Diarrhea has been found to be associated with a particularly high risk of adverse outcomes in the period following acute illness, such as mortality, re-hospitalization, and linear growth faltering.[4,5,7,8] Further, diarrhea is caused by a variety of microbial etiologies, and in settings where these infections are endemic, it is not clear which children should be prioritized for antibiotic administration.[7,17,18] However, little is known about the effects of antibiotic management for MSD on growth outcomes in the post-acute period following diarrhea. Understanding whether antibiotic treatment for MSD may protect children against longer term consequences of diarrheal disease on linear growth can inform clinical management of MSD in children who may be at high risk of linear growth faltering. Further, which groups of children are at highest risk of linear growth faltering in the months following MSD remains unclear. A clinically useful predictive model would identify host and clinical factors that indicate, at MSD presentation, a child's risk of linear growth faltering following the illness. This predictive model could have important implications for developing targeted interventions by identifying children at high risk of post-acute consequences on growth and who may benefit from targeted interventions, such as antibiotics, for improving longer term outcomes.

Once a targeted intervention has been developed, an economic evaluation is needed to translate the intervention into policy. Cost-effectiveness analysis is an important tool for guiding resource allocation and prioritizing populations likely to benefit most. Cost-effectiveness research is particularly important in SSA, where the overlapping burdens of high child mortality and limited health resources highlight the need to maximize the health impact of limited funds. In spite of its

importance in low-resource settings, a recent review found that only 4% of economic evaluations addressed low-income countries.[19] There is a need for more economic evaluation research in low-resource settings to ensure limited health funds are spent wisely.

One of the challenges to economic evaluation research in SSA is collecting quality cost data. Micro-costing leads to precise, patient-level cost data, though it depends on the availability of patient-level data at health facilities. This approach is recommended when costs are integral to a cost-effectiveness model or when an intervention is likely to impact resource use,[20,21] which may be expected for antibiotic interventions that may prevent morbidity (and therefore prevent costly hospitalizations) in addition to mortality and growth faltering. While there have been comparisons of gross- vs micro-costing approaches[22–24] and other methodologies,[25,26] little is known about which micro-costing methods are optimal for resource-limited settings in terms of accuracy and feasibility. A recent review found that economic evaluations in low-income countries more often employed micro-costing methods than those in middle- or high-income countries,[27] highlighting the need for understanding which micro-costing methods result in the most accurate cost data in low-resource settings.

The recently completed and currently ongoing trials described above[28–31] provide an important opportunity to assess the resource implications and health impacts of these antibiotic administration strategies, a cost-effectiveness analysis that will have timely implications for policy development. A cost-effectiveness model comparing targeted to MDA approaches will be a useful tool for policy decisions, and can be updated with new efficacy data as more results become available. Identifying the more cost-effective antibiotic administration strategy will allow policymakers in SSA to allocated budgets so as to produce greatest possible impact on child mortality in these resource-limited health systems.

Together, these research questions will provide actionable, novel data that will inform development and implementation of interventions targeting post-discharge mortality and growth faltering in SSA children.

CHAPTER 1

Determinants of Linear Growth Faltering among Children with Moderate-to-Severe Diarrhea in the Global Enteric Multicenter Study

ABSTRACT

Background

Moderate-to-severe diarrhea (MSD) in the first 2 years of life can impair linear growth. We sought to determine risk factors for linear growth faltering and to build a clinical prediction tool to identify children most likely to experience growth faltering following an episode of MSD.

Methods

Using data from the Global Enteric Multicenter Study of children 0-23 months old presenting with MSD in Africa and Asia, we performed log-binomial or log-Poisson regression to determine clinical and sociodemographic factors associated with severe linear growth faltering (loss of ≥ 0.5 length-for-age z-score [LAZ]). Linear regression was used to estimate associations with ΔLAZ. A clinical prediction tool was developed using backwards elimination of potential variables, and Akaike Information Criterion to select the best fit model.

Results

Of 5902 included children, mean age was 10 months, and 43.2% were female. Over the 90-day follow-up period, 24.2% of children had severe linear growth faltering and the mean ΔLAZ over follow up was -0.17 (standard deviation [SD]: 0.54). After adjustment for age, baseline LAZ, and site, several factors were associated with decline in LAZ: young age, acute malnutrition, hospitalization at presentation, non-dysenteric diarrhea, unimproved sanitation, lower wealth, fever, co-morbidity, or an IMCI danger sign. Compared to children 12-23 months old, those 0-6 months were more likely to experience severe linear growth faltering (adjusted prevalence ratio [aPR]: 1.97 [95% CI: 1.70, 2.28]), as were children 6-12 months of age (aPR: 1.72 [95% CI: 1.51, 1.95]). A prediction model that included age, wasting, stunting, presentation with fever and presentation with an IMCI danger sign had an area under the ROC (AUC) of 0.67 (95% CI: 0.64, 0.69). Risk scores ranged from 0-37, and a cut-off of 21 maximized sensitivity (60.7%) and specificity (63.5%).

Conclusion

Younger age, acute malnutrition, MSD severity, and sociodemographic factors were associated with short-term linear growth deterioration following MSD. Data routinely obtained at MSD may be useful to predict children at risk for growth deterioration who would benefit from interventions.

INTRODUCTION

Chronic malnutrition is highly prevalent among children under age five globally, with the greatest burden affecting children in low and middle-income countries (LMICs) in Africa and Asia.[32] Stunting, defined as height- or length-for-age (HAZ/LAZ) less than 2 standard deviations below the population standard mean[33] is an indicator of chronic malnutrition.[2] Fifteen percent of all deaths and 21% of disability-adjusted-life-years in children under 5 years have been attributed to stunting.[34] Stunting also has long term consequences, including impaired cognitive development, increased risk of non-communicable disease in adulthood and decreased economic productivity.[10]

Although the etiology of chronic malnutrition is multi-faceted, an estimated 13.5% of global stunting prevalence is attributable to diarrheal disease.[35] A meta-analysis of longitudinal studies in five LMICs reported a child's odds of stunting at 24 months of age increased by 16% with every 5% increase in incidence of diarrhea (odds ratio: 1.16 [95% confidence interval (95% CI): 1.07, 1.25]).[8] In addition, children in seven LMIC's across Africa and Asia who experienced moderate-to-severe diarrhea (MSD) lost significantly more height/length for age z-score (HAZ/LAZ) in the 2-3 months following the episode than age- and village- matched controls.[7]

Addressing linear growth faltering in children with MSD may be an important step towards reducing stunting and its long-term consequences. This may be particularly true for those under 24 months of age, as this is the critical time period in which most growth faltering occurs[36] and during which interventions are likely to be effective. However, it is unclear which groups of children are at highest risk. In addition, few interventions have been successful at mitigating the nutritional consequences of diarrhea.[37] Identifying risk factors for post-MSD linear growth faltering can inform which groups of children should be prioritized for inclusion in trials of potential interventions, and, once an effective intervention has been identified, to optimize the effectiveness of intervention delivery within programs by targeting children at high risk of growth faltering.

Using data from children under 24 months old with MSD enrolled in a previous large diarrhea etiology study (the Global Enteric Multicenter Study, or GEMS), we sought to identify determinants of linear growth faltering in the 60-90 days following presentation with MSD. We evaluated frequency and severity of linear growth faltering in this population and identified clinical, host, and socioeconomic factors associated with faltering in linear growth during the short-term follow up period. We also developed and validated a predictive model and risk scoring tool for estimating an individual child's risk of short-term growth faltering following MSD.

METHODS

Study setting and populations

GEMS1[7] was a large case-control study conducted between 2007 and 2011 in Bangladesh, India, Pakistan, Kenya, Mali, Mozambique, and the Gambia. GEMS enrolled MSD cases (children 0-59 months old seeking care at study health facilities for an episode of new [onset after ≥7 diarrhea-free days) and acute diarrhea [≥3 abnormally loose stools within the previous 24 hours with an onset within the previous 7 days] with at least one of the following characteristics: dehydration (presence of sunken eyes, loss of skin turgor, intravenous hydration administered or prescribed), dysentery (presence of visible blood in diarrhea), or clinical decision to admit to hospital]) and one to three village- and age-matched controls who had not had diarrhea in the previous 7 days for each case. Children presenting with prolonged (>7 days' duration) and persistent (>14 days' duration) diarrhea were excluded. GEMS included a single follow up visit predefined at 60 days (with an acceptable range of 50-90 days) following enrollment. Study clinicians performed physical exams and conducted interviews with caregivers at enrollment and at follow up to ascertain clinical, anthropometric, and sociodemographic factors. At enrollment (MSD presentation), weight and mid-upper arm circumference (MUAC) were measured at least 4 hours

after correction rehydration or when the child left the hospital. Child's length was measured 3 times at each visit, and median measures used in the analysis. Study clinicians also abstracted data from medical records if the child was hospitalized at enrollment.

This secondary analysis used the enrollment and follow up data of the MSD cases enrolled in GEMS, restricting to children under 24 months of age. Children were therefore included in this analysis if they were an MSD case, were under 24 months of age, and had both LAZ measurements available at enrollment and follow up; therefore, children who died or were lost to follow up were excluded. We also excluded children with implausible length/LAZ values (length at follow-up was less than enrollment; LAZ >7 or <-7 at enrollment or follow-up). Because use of MUAC is not widely recommended in children under 6 months of age, only MUAC measurements for children over 6 months of age were included in the analysis.

Variables and definitions

Outcomes

We defined faltering in linear growth using change in length-for-age z-score (ΔLAZ) between enrollment and follow up. Linear growth faltering was defined in two ways: (1) as a binary variable ($\Delta LAZ \geq 0.5$) and (2) as a continuous variable (ΔLAZ) with $\Delta LAZ<0$ being considered a loss.

Risk Factors

Risk factors examined in this analysis included clinical and sociodemographic factors. Factors included age (per date of birth in health records or Health and Demographic Surveillance System record), sex, admission to hospital at presentation, presentation with fever (axillary temperature > 37.5 F), co-morbidities per final diagnosis indicated on medical records, LAZ at presentation calculated according to WHO standards,[33] wasting (weight-for-length z-score [WLZ] < -2 using WHO standards, using post-rehydration weight), dysentery (discharge diagnosis of dysentery per managing clinician upon leaving the healthcare facility, or visible blood in stool observed by study staff, reported by caregiver at presentation, or observed in stool sample by laboratory staff), stunting (LAZ < -2 using WHO standards), and duration of diarrhea (caregiver reported number of days the diarrhea has lasted at presentation. Anthropometric z-scores were calculated using WHO Stata macro code.[38] Duration of diarrhea was defined as the duration of diarrhea at presentation plus duration of diarrhea after enrollment. Duration of diarrhea for the 7 days before enrollment was ascertained at enrollment (children with diarrhea lasting longer than 7 days were excluded at this point), and diarrhea duration for the 14 days following enrollment was ascertained with a memory aid suitable for groups of all literacy levels, which the caregiver returned at the 60-day follow up visit. Cessation of the enrollment episode was defined as two consecutive days in which diarrhea was not reported. Acute diarrhea was defined as diarrhea ≤ 7 days duration, prolonged diarrhea as diarrhea >7-13 days duration, and persistent as 14 days duration or more. Sociodemographic characteristics evaluated included access to improved water (caregiver report of the following: main source of drinking water for the household is piped into house or yard, public tap, tubewell, covered well, protected spring, rainwater, or borehole; is accessible within 15 min or less, roundtrip; and is available daily), access to improved defecation facility (caregiver report of access to the following: flush toilet, ventilated improved pit latrine with or without water seal, or pour flush toilet not shared with other households), caregiver handwashing (caregiver report of handwashing before eating, before handling child's food, after defecation, or after disposing of child's feces), wealth quintile (quintile of a wealth effects score calculated from asset ownership information reported by caregiver at enrollment[39]).

Data analysis

Risk factor model

Univariate and multivariable relative risk regression models specifying a binomial distribution or Poisson distribution if model failed to converge[40] with robust standard errors were used to estimate relative risks of severe linear growth faltering and 95% confidence intervals (95% CIs). Univariate and multivariable linear regression models with robust standard errors were used to estimate continuous ΔLAZ and 95% CIs associated with the exposure variables of interest. Multivariable models were adjusted *a priori* for age, site, and LAZ at enrollment.

Secondary analysis

Children who were missing LAZ measurements at one or both of the study visits were excluded from the primary analysis. We conducted a secondary analysis, in which we repeated the analysis of risk factors using imputed LAZ values for children in whom follow-up LAZ was missing due to loss to follow up or death.[41] The "mi monotone" suite of Stata commands was used for multiple imputation for monotone missing data, which assume missingness at random conditional on observed characteristics. Imputation models included linear regression to impute ΔLAZ and poisson regression to impute severe linear growth faltering. Variables were selected for inclusion in the imputation if they were associated with missingness, per χ^2 tests for categorical variables and t-tests for continuous variables. Diagnostics of the imputation models included examining imputed values for reasonableness (whether the values were plausible and scientifically sensible given the covariates in the model), and comparing distributions of imputed vs observed values. All analyses were conducted in Stata 14.

Clinical Prediction Tool

In addition to a risk factor model, a clinical prediction model was developed to identify the combinations of factors that best predicted a child's risk of severe linear growth faltering in the 50-90 days following MSD. We included only the characteristics in Table 1 that are easily collectible in a clinical setting in the prediction model. The data were randomly divided into separate derivation and validation datasets of equal size, and t-tests or χ^2 tests used to identify differences in baseline characteristics between the datasets. A backwards elimination approach[42,43] was used to develop the model, in which all candidate variables are included and eliminated based on statistical significance ($p \leq 0.1$). We used Akaike Information Criterion (AIC), a measure of model fit that penalizes larger models and thus attempts to reduce overfitting, to select the best fit model. We translated the best-fit model into a practical risk scoring tool by assigning values for each predictor based on the beta-coefficients from the model as described elsewhere.[44] The sum of risk scores for each parameter was the total risk score for each child. To validate the model, the risk score was applied to the validation cohort, and AUC performance and Brier score were compared with the derivation cohort.

We assessed the ability of the risk score to discriminate between children with and without severe linear growth faltering, with risk score as the sole predictor, using receiver operating characteristic (ROC) analysis to calculate area under the curve (AUC).[45] We also estimated Brier scores to quantify the difference between the predicted and actual outcomes; useful prediction models have Brier scores < 0.25.[45] Risk scores were dichotomized into the most predictive categories using the cut-point identified in ROC analysis, which optimizes sensitivity and specificity. Positive and negative predictive values (PPV, NPV) were also calculated.

RESULTS

Among the 9439 children with MSD who were enrolled in the GEMS study, 5902 surviving children under 24 months of age had follow-up LAZ values and were included in the primary analysis (Figure 1) Median age of included children was 10 months (interquartile range: 7-15) and 43.2% were female (Table 1). Distribution across the 7 sites was similar to that in the parent study: 647 (10.9%) in the Gambia, 1188 (20.1%) in Mali, 375 (6.3%) in Mozambique, 850 (14.4%) in Kenya,

1170 (19.8%) in India, 962 (16.4%) in Bangladesh, and 727 (12.3%) in Pakistan. Approximately 23% (n=1375) of children presented with dysentery, 94.0% of whom were given or prescribed an antibiotic in the health facility (whereas 75.2% of children without dysentery were given or prescribed an antibiotic). Twenty-eight percent presented with fever and 19.3% were hospitalized at presentation. One in four children presenting with MSD were stunted at presentation and one in five were wasted. Approximately 41.2% (n=2,433) of these children under 24 months of age experienced a subsequent diarrhea episode during the follow up period, per caregiver report at the follow up visit.

Mean ΔLAZ between enrollment and follow up was -0.17 (standard deviation [SD]: 0.54). Median ΔLAZ was -0.20 (interquartile range: -0.49, 0.09), and 24.2% developed severe linear growth faltering (loss of ≥ 0.5 LAZ) during the 90-day follow-up period. Notably, 85.5% of these children who lost ≥ 0.5 LAZ during follow up were not stunted at MSD presentation, and 75.2% of these were not wasted. Children whose caregivers reported experienced a subsequent diarrhea episode during follow up lost slightly more LAZ than those who did not (ΔLAZ = -0.19) than those who did not (ΔLAZ -0.15) (p-value from t-test = 0.02).

Risk factor analysis

ΔLAZ

Age and nutritional status at MSD presentation, but not sex, were associated with ΔLAZ. Children 0-6 months old and those >6-12 months old both lost approximately 0.09 more LAZ than children >12-23 months ($a\beta_{0\text{-}6\ mo}$: -0.08 [95% CI: -0.12, -0.04]; $a\beta_{>6\text{-}12\ mo}$: -0.09 [95% CI: -0.12, -0.06]), adjusting for baseline LAZ and site. (Table 2 and Figure 2). Figure 2a depicts the pattern of ΔLAZ by age, demonstrating that the magnitude of LAZ loss decreased with each month gain in age. Children with higher baseline LAZ values experienced the greatest loss in LAZ (Figure 2c), in an inverse relationship pattern; magnitude of LAZ loss decreased consistently with each unit decrease in LAZ (aβ: -0.10 [95% CI: -0.11, -0.09]). Children stunted at MSD presentation gained LAZ compared to their non-stunted counterparts (aβ: 0.21 [95% CI: 0.18, 0.24]) whereas wasted children lost an average of 0.19 LAZ more than children without (95% CI: -0.23, -0.16). Among children over 6 months of age, those with MUAC of ≥12.5 cm, children with MUAC < 12.5 cm lost 0.11 more LAZ (95% CI: -0.15, -0.07]) after accounting for age, site, and baseline LAZ. Children who had a final diagnosis of malnutrition per discharge medical records lost 0.21 more LAZ than those who did not (95% CI: -0.26, -0.13). Males' ΔLAZ was similar to that of females (aβ: 0.01 [95% CI: -0.02, 0.04]).

Several clinical factors at MSD presentation were associated with linear growth faltering. Children who were hospitalized at enrollment lost 0.06 more LAZ than those who were not (95% CI: -0.10, -0.02) and those who presented with fever lost 0.08 more LAZ (95% CI: -0.12, -0.04) in adjusted analysis. Children presenting with at least one Integrated Management of Childhood Illness (IMCI) danger sign lost more LAZ than those who had none (aβ: -0.05 [95% CI: -0.08, -0.02]). Presentation with any co-morbidity was associated with losing more LAZ (aβ: -0.07 [95% CI: -0.10, -0.03]), but this association was likely driven by one specific co-morbidity: among the co-morbidities documented in medical records, only a discharge diagnosis of malnutrition was associated with loss of LAZ. Compared to children with non-dysenteric MSD, those presenting with dysentery lost less LAZ (aβ: 0.05 [95% CI: 0.01, 0.09]). Prolonged or persistent MSD (using caregiver-recalled duration of diarrhea at follow up) was also not associated with linear growth faltering.

In addition to clinical factors, several baseline socio-demographic factors were also protective against loss of LAZ. Children whose caregivers reported access to an improved defecation facility

lost substantially less LAZ than those without access to this level of sanitation (aβ: 0.07 [95% CI: 0.02, 0.11]). In addition, children in the highest wealth quintiles lost less LAZ than those in lowest quintile ($a\beta_{wealthiest}$: 0.10 [95% CI: 0.05, 0.14]; $a\beta_{second\ wealthiest}$: 0.04 [95% CI: 0.002, 0.09]).

Using multiple imputation resulted in an additional 845 children being added to the dataset, including 165 who died in the study period, resulting in 6764 included in the analysis with imputed outcomes. An additional file presents distribution of imputed versus observed outcomes (Additional File 1 Figure 1), as well as baseline characteristics between children with imputed versus observed outcomes (Additional File 1 Table 1). Risk factors for ΔLAZ calculated using imputed values were similar to the complete-case analysis (Addition File 1 Table 2), with no substantial differences in effect size or statistical significance.

Severe linear growth faltering

Prevalence of severe linear growth faltering by age and nutritional status at presentation followed a similar pattern to that of ΔLAZ (Table 2 and Figure 2c/d). We also depict the pattern of prevalence of severe linear growth faltering by interactions between age and baseline LAZ (Figure 3). Unlike our results for ΔLAZ, female children were 10% less likely to experience severe linear growth faltering than males (aPR: 0.90 [95% CI: 0.81, 0.99]). Hospitalization, fever, and at least one IMCI danger sign were significant risk factors for severe linear growth faltering, as they were for ΔLAZ. Although the absence of dysentery was associated with ΔLAZ, non-dysenteric MSD did not emerge as a statistically significant risk factor for severe linear growth faltering (aPR: 0.88 [95% CI: 0.75, 1.02]) but the prevalence ratio did approach statistical significance (p-value=0.09). The socio-demographic factors examined (improved water source or defecation facility, and wealth quintile) were not statistically significantly associated with severe linear growth faltering in our analyses.

Results for the secondary analysis including imputed values were similar (Additional File 1 Table 2) for all risk factors other than sex, which was not significantly associated with severe linear growth faltering in the imputed models (aPR: 0.91 [95% CI: 0.82, 1.01]), though the effect size was similar to that of the primary analysis and p-value approached significance (p-value = 0.08).

Prediction model results

In the derivation dataset of 2951 children, there were 713 who experienced severe linear growth faltering (24.2%). The validation cohort also consisted of 2951 children, of whom 713 (24.2%) experienced severe linear growth faltering. There were no statistically significant differences in any demographic or clinical characteristics between the derivation and validation datasets (Table 3).

The final prediction model included age, presentation with fever, wasting at enrollment, stunting at enrollment, and presentation with at least one IMCI danger sign. These factors were used to create a risk score for severe linear growth faltering for each child (Figure 4). In the overall cohort, risk scores ranged from 0 to 37, and the median risk score was 19 (interquartile range: 14 - 24) (Figure 5). Mean variance inflation factor was 2.6. Model fit was similar in the derivation and validation datasets (AUC: 0.68 (95% CI: 0.65, 0.70); 0.67 (95% CI: 0.64, 0.69), respectively) (Figure 6). In the derivation dataset, a cut-off of 21 optimized both sensitivity and specificity 60.7% and 63.5%, respectively. In the validation dataset, the sensitivity, specificity, PPV, and NPV were of the cut-off point of 21 in the validation dataset were 59.5% and 63.1%, 33.9% and 83.0% respectively (Table 4). Also in the validation dataset, the risk score identified children most likely to severely growth falter better than any individual predictive factor: age (AUC = 0.37 [95% CI: 0.35, 0.39]); presentation with fever (AUC = 0.53 [95% CI: 0.51, 0.54]); stunting (AUC = 0.43 [95%

CI: 0.42, 0.45]); wasting (AUC = 0.52 [95% CI: 0.50, 0.54]); or presentation with at least 1 IMCI danger sign (AUC = 0.55 [95% CI: 0.53, 0.57]).

DISCUSSION

In this analysis nested in the multi-center GEMS study, we found that over one-fifth of children under 24 months with MSD had linear growth faltering at 90-days following the MSD episode. We identified several risk factors for linear growth faltering, including age, fever, general IMCI danger sign, and nutritional status. We found that some of these factors in combination yielded reasonable predictive value to identify children likely to experience severe linear growth faltering following MSD. We found that the majority of children who experienced linear growth faltering were not stunted at diarrhea presentation. Stunting status at diarrhea presentation may not identify all children who are at risk for linear growth declines following diarrhea. Using these other clinical factors to predict linear growth faltering may result in earlier and more complete identification of children who are on a trajectory of linear growth declines, comparing to using only stunting status at diarrhea presentation to predict post-diarrhea growth declines, and thus may be useful for targeting interventions to prevent stunting.

Linear growth faltering followed patterns determined by age and baseline LAZ. The older the child, or the lower the LAZ value, the lower the probability that the child will lose LAZ. Growth in early life is rapid and decreases as the child ages.[46,47] Correspondingly, risks of linear growth faltering decrease as children age, with the highest risk occurring before 12 months. Our findings are consistent with previous work noting the substantial losses of LAZ in early life [36] and suggest that interventions may confer the most benefit within this critical period. This growth pattern also underscores methodological considerations for analyses of linear growth faltering. Children in the youngest age groups have the highest growth velocity, and therefore have the greatest opportunity to lose or gain LAZ. Challenges in ascertaining and interpreting losses in linear growth highlight the need for standardization in definitions of linear growth faltering and research to assess the clinical relevance of different magnitudes of loss in LAZ by different age groups.

Similar to the patterns of LAZ loss by age, LAZ values that are already low (below 0) also represent decreased potential to lose more LAZ. We have described how losses in LAZ increase consistently with higher LAZ. While stunting status or low LAZ values may not identify children who are at risk for *further* linear growth deterioration, children who are already stunted are at high risk of the health and cognitive detriments associated with chronic malnutrition. A modest loss in LAZ in this group may prove to have more health consequences in already stunted children than a loss of greater magnitude in non-stunted children at diarrhea presentation.

We identified host, clinical, and environmental characteristics that were significantly associated with short-term linear growth faltering. Acute malnutrition (measured either by MUAC or WLZ) was significantly associated with subsequent growth faltering. Ponderal growth has previously been found to be associated with linear growth. A longitudinal analysis of birth cohorts from the United States, Ghana, and Honduras reported that WLZ was positively correlated with length gain,[48] as did a cohort study of Jamaican 9-24 month old stunted children.[49] Additionally, a study in the West Indies reported that severely malnourished children needed to attain ≥ 85% WLZ before they began to gain LAZ.[50] These studies suggest ponderal growth may precede linear growth, as weight loss reflects a lack of available nutrients needed to sustain linear growth. It is also possible the higher risks of severe linear growth faltering we observed in acutely malnourished children may be due to higher rates of subsequent diarrhea episodes during the follow up period. Previous research has reported higher incidence of diarrhea in acutely malnourished children.[51,52], though we did not have data on diarrhea during follow up to examine this hypothesis. Acutely malnourished children presenting with MSD may thus be an easily

identifiable population who may benefit from nutritional interventions that protect against linear growth faltering.

Presentation with fever was associated with linear growth faltering as has been shown previously.[53] Fever may be a sign of more severe diarrhea, which may be associated with linear growth faltering. This is supported by the finding that children with MSD who were hospitalized at presentation were at higher risk of linear growth faltering than those who were not. Finally, the presence of any IMCI danger sign at MSD presentation was also associated with a loss of more LAZ. Studies have demonstrated the potential of IMCI programs for improving quality of care and child survival.[54–56] However, a Cochrane review of the effectiveness of IMCI programs reported little to no benefit on stunting or wasting[55] which could reflect the lack of effective interventions for improving nutritional status upon identification of high-risk children.

In our analysis, children presenting with dysentery had lower risks of linear growth faltering than those with non-dysenteric MSD. This finding was unexpected and differs from that of other studies that found dysentery, or specific pathogens known to cause dysentery, to be associated with risk for linear growth faltering.[57–59] Our detection of a *reduced* risk associated with dysentery may be related to clinical management. WHO guidelines recommend antibiotics for dysentery[60], and in our data, children presenting with dysentery were more likely to receive an antibiotic than those without. It is unclear whether antibiotic management of MSD alters growth[37]; some research has reported growth-promoting effects of antibiotic treatment on length and weight in children in LMICs.[14,61] Clinical trial data will be needed for evaluating the effectiveness of antibiotic management of MSD for protecting against subsequent linear growth faltering.

We found that children in lower wealth quintiles had the highest rates of linear growth faltering. Poverty is a well-established underlying cause of childhood stunting. There are large disparities in stunting rates by wealth quintile within LMICs, with child stunting rates in lowest wealth quintiles as much as 13 times higher than in the highest.[62] Socioeconomic factors are the most consistently identified correlates of stunting,[63] and it has been estimated that every 10% increase in national gross domestic production per person would result in a 6% decrease in stunting prevalence.[64] Economic development may be influential in protecting children with MSD against linear growth faltering.[65] We found that children in households without access to improved defecation facilities lost more LAZ. Greater exposure to environmental pathogens may place children at higher risk of linear growth faltering, as pathogen-specific diarrhea[58,59] and asymptomatic pathogen carriage[66–68] have been found to be associated with linear growth faltering. Unimproved WASH may also contribute to environmental enteric dysfunction (EED), which is strongly associated with linear growth faltering and thought to play a central role in stunting.[69,70] However, WASH interventions have not yielded consistent benefits. While a review of stunting in 137 LMICs using Global Burden of Disease data reported unimproved sanitation to be a leading cause of stunting,[35] a Cochrane review reported only modest benefits of WASH on child length but limited availability and quality of evidence.[71] Large clinical trials of WASH interventions did not detect a benefit on child growth[72–74].

When considering which risk factors best predicted likelihood of linear growth faltering, age, stunting, wasting, fever and presence of any IMCI danger sign emerged as the most important. This prediction model performed reasonably well in internal validation, but external validation would further improve the model. The risk score model performed better than any individual predictive factor, suggesting that the combination of these factors is more useful for identifying children at risk of severe linear growth faltering than any of these variables individually. We identified the risk score cut-point that maximizes sensitivity and specificity, but the cut-point used in practice should be weighed against the costs or negative consequences of potential

interventions. This predictive model uses only easily collected clinical data routinely documented at diarrhea presentation, and such a risk score could be useful for identifying children at highest risk for inclusion in trials of interventions to reduce linear growth faltering and ultimately may prove useful in determining how to best target successful interventions once benefit is demonstrated, by identifying high-risk children who stand to benefit from such an intervention or be monitored more closely following MSD.

There have been few studies to our knowledge that identify risk factors of linear growth faltering in children following an episode of MSD. Our study contributes data on this important topic, using a large, multi-country cohort with a rigorous study design and data collection practices. There are several limitations to our analysis as well. Data on birth size, HIV status, and previous and subsequent diarrhea episodes were not available in the parent study, which may be relevant to this secondary analysis. Our analysis assessed short-term effects (3 months) only. It has been reported that catch-up growth is possible following a diarrhea episode if no subsequent diarrhea episodes are experienced,[75] and it is possible that some of the growth deficits we observed were transient. The risk and predictive factors we have identified for short-term losses in LAZ may or may not be the same factors associated with longer term growth declines. However, we found that a substantial proportion of these children presenting with MSD experienced a repeated diarrhea episode in the subsequent 50-90 days, and this additional growth insult may have precluded catch-up growth for this subset, who may have continued on a linear growth decline. Longer follow-up studies will be important for assessing sustained linear growth deficits associated with diarrhea. The cut-off of 0.5 LAZ for our definition of severe linear growth faltering is arbitrary, and the clinical implications of this magnitude of loss are unclear. Additionally, all definitions used implicitly assume the impact of LAZ loss is the same, irrespective of age or enrollment LAZ. We adjusted for age and LAZ at baseline in our analysis, but difficulties remain with interpreting the health detriments of these outcomes.

CONCLUSION

Children presenting with MSD that are acutely malnourished, under 12 months of age, presenting with more severe disease (as indicated by hospitalization, presence of fever, or IMCI danger signs), and those living with limited access to improved sanitation may be at higher risk of linear growth faltering following MSD. To identify children for inclusion in further trials and to guide clinical decision-making for close monitoring of high-risk children or targeting an intervention once an effective intervention has been identified, age, nutritional status, and signs of disease severity may be useful to identify children at highest risk.

TABLES AND FIGURES

Figure 1: Flowchart of included subjects

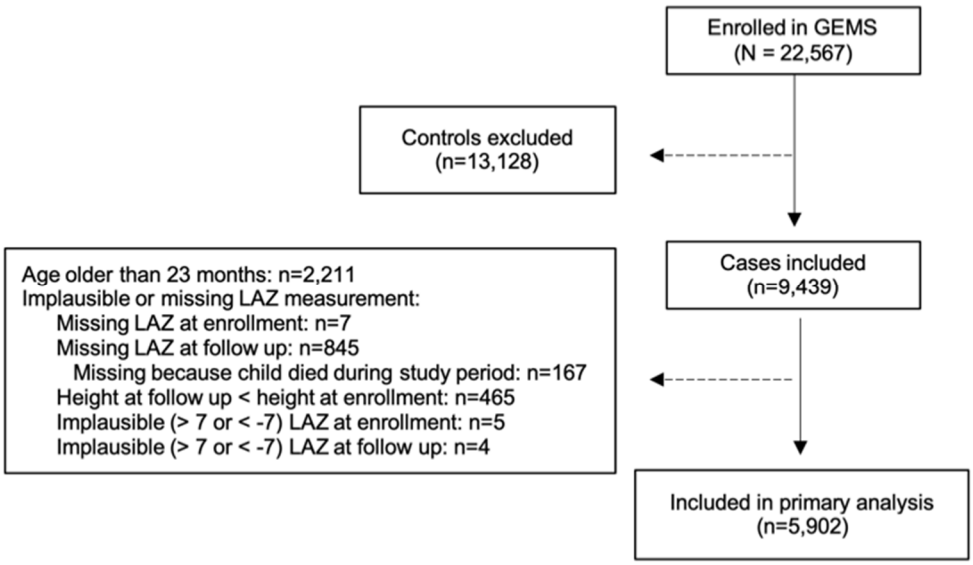


Table 1. Baseline characteristics of children with MSD included in this GEMS analysis

	n(%) or median (interquartile range)	
Sociodemographic characteristics		
Age, months	10	(7-15)
0-6 months	1075	(18.2%)
>6-12 months	2282	(38.7%)
>12-23 months	2545	(43.1%)
Site		
the Gambia	647	(10.9%)
Mali	1188	(20.1%)
Mozambique	375	(6.3%)
Kenya	850	(14.4%)
India	1170	(19.8%)
Bangladesh	962	(16.4%)
Pakistan	727	(12.3%)
Female	2557	(43.2%)
Access to improved water	2733	(46.2%)
Access to improved sanitation[i]	1111	(18.8%)
Wealth quintile[39]	-0.08	(-0.71, 0.59)
Clinical characteristics at presentation		
Stunting	1405	(23.7%)
Wasting	1240	(21.0%)
Severe wasting[ii]	427	(7.21%)
MUAC < 12.5 cm among 6-23 mos	794	(16.4% of 4842 children)
Fever	1668	(28.2%)
Current breastfeeding < 6 mos		
Exclusive	398	(37.0%)
Partial	633	(58.8%)
None	46	(4.3%)
Hospitalized at presentation	1141	(19.3%)
Dysentery at presentation[iii]	1375	(23.3%)
≥1 IMCI general danger sign	3426	(57.9%)
Presented with at least 1 co-morbidity[iv]	1911	(32.3%)

Pneumonia	390	(6.6%)
Malaria	1395	(23.6%)
Malnutrition	305	(5.2%)
Other invasive bacterial infection	70	(1.2%)
Upper respiratory tract infection	7	(0.1%)

[i] Flush toilet, ventilated improved pit latrine with or without water seal, or pour flush toilet not shared with other households

[ii] Severe wasting defined as weight-for-length z-score < -3

[iii] Visible blood in stool observed by study staff or reported by caregiver at presentation; discharge diagnosis of dysentery per managing clinician upon leaving the healthcare facility; or observed in stool sample by laboratory staff

[iv] Per discharge diagnoses documented on medical records

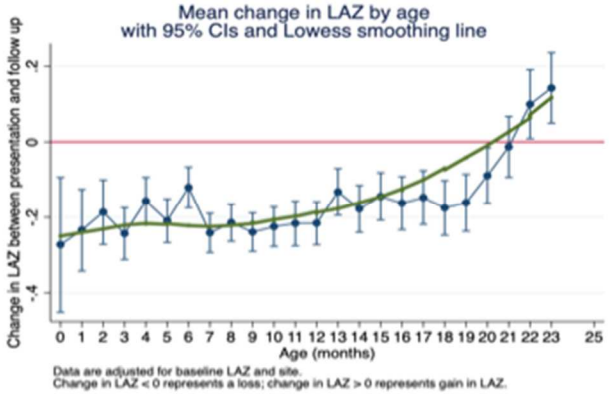
Table 2. Risk factors for linear growth faltering among children 0-23 months old with MSD with complete outcome data. Statistically significant results (p <0.05) are bolded. Asterisks (*) denote results from a robust Poisson model rather than log-binomial model.

	ΔLAZ				Severe linear growth faltering			
	mean	SD	Crude difference in change in LAZ	Adjusted for age, site, and baseline LAZ[v]	No. with outcome	Prevalence of loss of ≥0.5 LAZ	Crude relative risks	Adjusted for age, site, and baseline LAZ[v]
Age[vi]								
0-6 mo	-0.23	0.95	**-0.13 (-0.17, -0.09)**	**-0.08 (-0.12, -0.04)**	366	34.1%	**2.24 (1.98, 2.17)**	**1.97 (1.70, 2.28)***
>6-12 mo	-0.23	0.54	**-0.13 (-0.16, -0.10)**	**-0.09 (-0.12, -0.06)**	674	29.5%	**1.94 (1.74, 2.17)**	**1.72 (1.51, 1.95)***
>12-23 mo	-0.10	0.44	Reference	Reference	387	15.2%	Reference	Reference
Stunting[vii]								
No	-0.22	0.51	Reference	Reference	1220	27.1%	Reference	Reference
Yes	0.0004	0.62	**0.23 (0.19, 0.26)**	**0.21 (0.18, 0.24)**	207	14.8%	**0.55 (0.48, 0.62)**	**0.60 (0.51, 0.70)***
Sex								
Male	-0.17	0.58	Reference	Reference	847	19.6%	Reference	Reference
Female	-0.17	0.50	-0.01 (-0.03, 0.02)	0.01 (-0.02, 0.04)	588	17.7%	0.92 (0.84, 1.01)	**0.90 (0.81, 0.99)***
Wasting								
No	-0.15	0.55	Reference	Reference	1073	23.0%	Reference	Reference
Yes	-0.25	0.50	**-0.10 (-0.14, -0.07)**	**-0.19 (-0.23, -0.16)**	354	28.6%	1.24 (1.10, 1.40)	**1.35 (1.20, 1.53)**
MUAC (among 6-23 mos)								
≥12.5	-0.16	0.50	Reference	Reference	870	21.6%	Reference	Reference
<12.5 cm	-0.17	0.49	-0.02 (-0.05, 0.02)	**-0.11 (-0.15, -0.07)**	191	24.2%	1.12 (0.96, 1.31)	**1.36 (1.15, 1.62)**
Current breastfeeding (among < 6 mos)								
Exclusive	-0.24	0.78	Reference	Reference	140	31.6%	Reference	Reference
Partial	-0.21	0.69	0.03 (-0.05, 0.11)	-0.01 (-0.10, 0.08)	299	32.1%	1.02 (0.86, 1.20)	1.13 (0.90, 1.42)*
None	-0.28	0.75	-0.03 (-0.22, 0.15)	-0.14 (-0.32, 0.04)	25	37.9%	1.20 (0.85, 1.68)	1.49 (0.96, 2.32)*
Diarrhea type[viii]								
Acute	-0.17	0.50	Reference	Reference	671	22.6%	Reference	Reference
Prolonged	-0.18	0.54	-0.01 (-0.04, -0.02)	-0.003 (-0.03, 0.03)	462	25.4%	1.12 (1.00, 1.27)	1.04 (0.92, 1.17)*
Persistent	-0.15	0.58	0.03 (-0.02, 0.07)	0.03 (-0.01, 0.08)	151	24.3%	1.08 (0.90, 1.29)	0.98 (0.81, 1.17)*
Hospitalized at enrollment								
No	-0.17	0.53	Reference	Reference	1122	17.4%	Reference	Reference
Yes	-0.20	0.60	-0.03 (-0.07, 0.002)	**-0.06 (-0.10, -0.02)**	313	25.6%	**1.35 (1.21, 1.50)**	**1.35 (1.18, 1.56)***
Presentation with fever								
No	-0.23	0.55	Reference	Reference	1122	22.8%	Reference	Reference
Yes	-0.16	0.54	**-0.08 (-0.12, -0.04)**	**-0.08 (-0.12, -0.04)**	304	31.1%	**1.36 (1.22, 1.52)**	**1.35 (1.18, 1.53)***
Presentation with dysentery								
No	-0.18	0.55	Reference	Reference	1117	24.7%	Reference	Reference
Yes	-0.14	0.54	**0.03 (0.001, 0.7)**	**0.05 (0.01, 0.09)**	310	22.6%	0.91 (0.82, 1.02)	0.88 (0.75, 1.02)*
Co-morbidities								
None	-0.16	0.55	Reference	Reference	915	22.9%	Reference	Reference
Any	-0.19	0.52	-0.03 (-0.06, 0.003)	**-0.07 (-0.10, -0.03)**	512	26.9%	**1.17 (1.07, 1.29)**	**1.17 (1.02, 1.35)***

Pneumonia	-0.17	0.52	-0.002 (-0.06, 0.05)	-0.02 (-0.08, 0.03)	89	22.9%	0.94 (0.78, 1.14	0.88 (0.70, 1.09)*
Malaria	-0.19	0.53	-0.03 (-0.06, 0.002)	-0.03 (-0.07, 0.01)	390	28.0%	**1.22 (1.11, 1.35)**	**1.18 (1.02, 1.37)***
Malnutrition	-0.20	0.46	-0.03 (-0.09, 0.03)	**-0.19 (-0.26, -0.13)**	77	25.3%	1.05 (0.86, 1.28)	**1.50 (1.18, 1.90)***
Other bacterial infection	-0.23	0.63	-0.06 (-0.19, 0.07)	-0.01 (-0.14, 0.11)	27	39.1%	**1.63 (1.21, 2.20)**	1.26 (0.85, 1.85)*
Upper respiratory tract infection	-0.11	0.61	0.06 (-0.34, 0.46)	0.08 (-0.31, 0.47)	1	14.3%	0.59 (0.103.63)	0.54 (008, 3.83)*
IMCI danger signs								
None	-0.14	0.54	Reference	Reference	505	20.3%	Reference	Reference
At least 1	-0.19	0.54	**-0.05 (-0.08, -0.02)**	**-0.05 (-0.08, -0.02)**	922	27.0%	**1.33 (1.21, 1.46)**	**1.30 (1.16, 1.46)***
3 signs present	-0.13	0.71	0.02 (-0.12, 0.16)	-0.01 (-0.12, 0.15)	15	24.6%	1.21 (0.77, 1.46)	1.21 (0.73, 2.04)*
2 signs present	-0.20	0.56	**-0.05 (-0.09, -0.02)**	**-0.05 (-0.09, -0.01)**	295	27.7%	**1.36 (1.20, 1.54)**	**1.25 (1.07, 1.46)***
1 sign present	-0.19	0.53	**-0.05 (-0.08, -0.01)**	**-0.05 (-0.08, -0.02)**	611	26.7%	**1.31 (1.19, 1.46)**	**1.32 (1.17, 1.50)***
Access to improved water								
No	-0.16	0.55	Reference	Reference	779	24.5%	Reference	Reference
Yes	-0.18	0.54	-0.02 (-0.05, 0.01)	**-0.04 (-0.07, -0.002)**	648	23.8%	0.97 (0.87, 1.08)	1.06 (0.93, 1.22)*
Improved defecation facility								
No	-0.18	0.54	Reference	Reference	1168	24.4%	Reference	Reference
Yes	-0.15	0.53	0.03 (-0.01, 0.06)	**0.07 (0.02, 0.11)**	259	23.4%	0.96 (0.84, 1.10)	0.87 (0.74, 1.03)*
Wealth index								
Lowest quintile	-0.18	0.51	Reference	Reference	282	23.8%	Reference	Reference
Second lowest	-0.20	0.58	-0.02 (-0.06, 0.02)	-0.02 (-0.06, 0.03)	327	26.9%	1.13 (0.98, 1.29)	1.09 (0.92, 1.28)*
Middle	-0.17	0.52	0.01 (-0.03, 0.06)	0.02 (-0.02, 0.07)	287	24.0%	1.01 (0.87, 1.16)	0.98 (0.82, 1.15)*
Second highest	-0.16	0.51	0.02 (-0.02, 0.07)	**0.04 (0.002, 0.09)**	258	22.2%	0.93 (0.80, 1.08)	0.94 (0.79, 1.11*
Highest quintile	-0.14	0.59	**0.05 (0.002, 0.09)**	**0.10 (0.05, 0.14)**	270	23.6%	0.99 (0.86, 1.15)	0.88 (0.74, 1.04)*

[v] Analyses of age and stunting were not adjusted for age and baseline LAZ, respectively
[vi] Analysis of age as a risk factor was not adjusted for age
[vii] Analysis of stunting was not adjusted for baseline LAZ
[viii] Data on duration of diarrhea for the 7 days before enrollment were ascertained at enrollment (children with diarrhea lasting longer than 7 days were excluded at this point), and data on diarrhea duration for the 14 days following enrollment were ascertained with a memory aid suitable for groups of all literacy levels, which the caregiver returned at the 60-day follow up visit

Figure 2: Linear growth faltering following an episode of moderate-to-severe diarrhea by age and baseline LAZ



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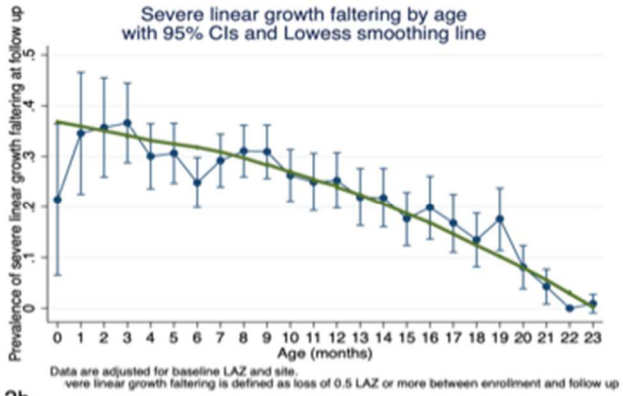

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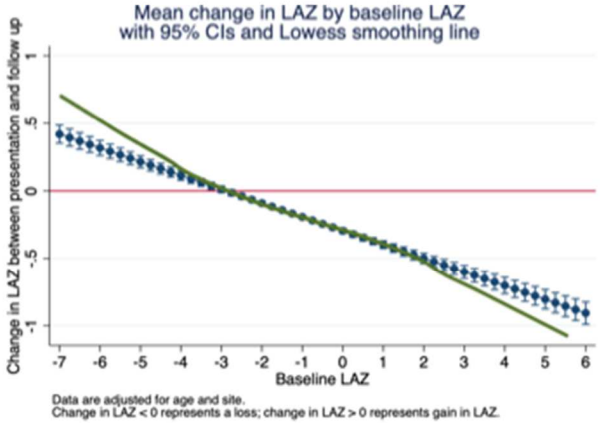

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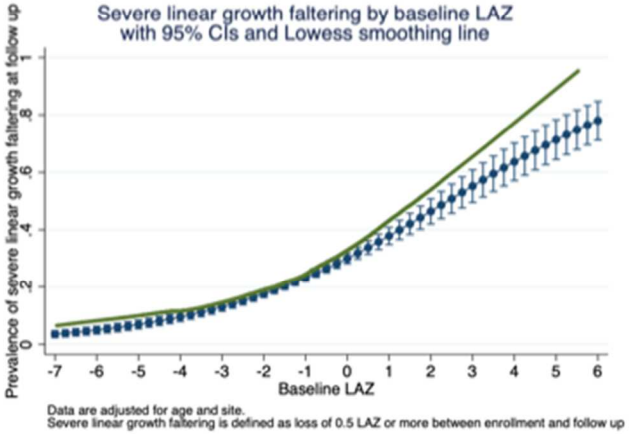

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Figure 3: Risk of linear growth faltering in terms of interactions between age and baseline LAZ)

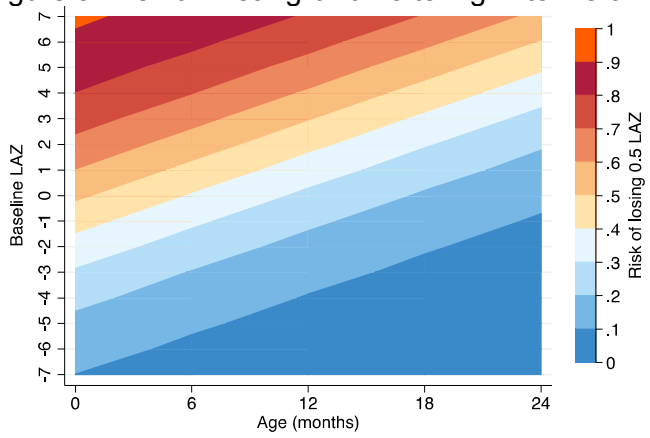


Figure 4: A risk scoring tool for predicting risk of linear growth faltering among children presenting with MSD

Risk factor	Value per factor	Score
Age		
Child's age in months	23 – age*	
Presentation with fever		
Fever	5	
No fever	0	
Stunting status		
Stunted (LAZ < -2)	0	
Not stunted (LAZ > -2)	6	
Wasting status		
Wasted (WLZ < -2)	5	
Not wasted (WLZ > -2)	0	
Presentation with at least 1 IMCI danger sign		
At least 1 danger sign	3	
No danger signs	0	
Total risk score		

**For example: an 18 month old would have a value of 23 – 18 = 5*

Figure 5: Distribution of risk scores among all children with complete outcome data (n= 5902)

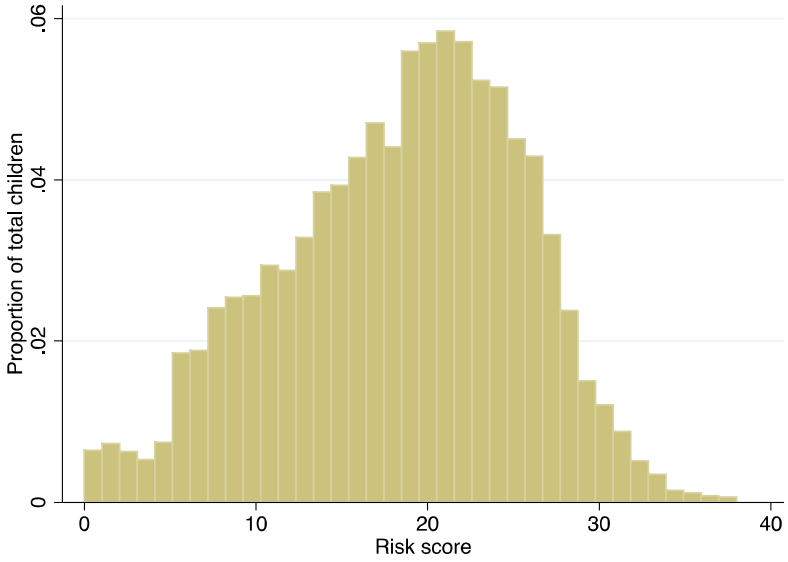


Figure 6: ROC curve of predicted risks of severe linear growth faltering using risk scores in the derivation cohort

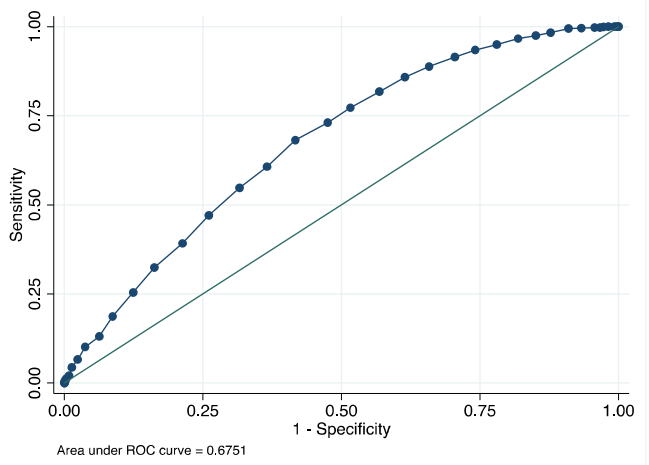


Table 4. Sensitivity, specificity, and predictive values of risk score at different cut-points in the derivation cohort

	Risk score cut-point				
	≥7	≥14	≥21	≥28	≥35
No. of children (% of total [5902])	5587 (94.7%)	4467 (75.7%)	2501 (42.4%)	438 (7.4%)	16 (0.3%)
Sensitivity	99.6%	91.4%	60.7%	13.1%	0.4%
Specificity	6.7%	29.5%	63.5%	93.7%	99.9%
Positive Predictive Value	25.3%	29.2%	34.6%	39.7%	60.0%
Negative Predictive Value	97.4%	91.4%	83.5%	77.2%	75.9%

Additional File 1 Table 1. Enrollment characteristics of GEMS cases included in the present analysis of growth faltering

	Children with complete data N=5902	Children with imputed outcomes N=845	p-value for difference
	n(%) or median (interquartile range)	n(%) or median (interquartile range)	t-test or chi2
Sociodemographic characteristics			
Age, months	10 (7-15)	10 (7-15)	P=0.1002
0-6 months	1075 (18.2%)	47 (5.6%)	
>6-12 months	2282 (38.7%)	349 (41.2%)	P=0.288
>12-23 months	2545 (43.1%)	343 (40.5%)	
Site			
the Gambia	647 (10.9%)	124 (14.6%)	
Mali	1188 (20.1%)	207 (24.4%)	
Mozambique	375 (6.3%)	108 (12.8%)	
Kenya	850 (14.4%)	87 (10.3%)	**P<0.0001**
India	1170 (19.8%)	54 (6.4%)	
Bangladesh	962 (16.35%)	21 (2.5%)	
Pakistan	727 (12.3%)	246 (29.0%)	
Female	2557 (43.2%)	385 (45.4%)	P=0.195
Access to improved water	2733 (46.2%)	283 (33.4%)	**P<0.0001**
Access to improved sanitation[ix]	1111 (18.8%)	183 (21.6%)	P=0.056

Wealth quintile[39]	-0.08	(-0.71, 0.59)	-0.27	(-0.87, 0.36)	**P<0.0001**
Clinical characteristics at presentation					
Stunting	**1405**	**(23.7%)**	**292**	**(34.5%)**	**P<0.0001**
Wasting	**1240**	**(21.0%)**	**283**	**(33.4%)**	**P<0.0001**
Severe acute malnutrition	**427**	**(7.21%)**	**130**	**(15.4%)**	**P<0.0001**
MUAC < 12.5 cm among 6-23 mos	**794**	**(16.4% of 4842)**	**194**	**(28.0% of 692)**	**P<0.0001**
Fever	**1668**	**(28.2%)**	**284**	**(33.5%)**	**P=0.002**
Current breastfeeding < 6 mos					
Exclusive	398	(37.0%)	104	(12.3%)	**P<0.0001**
Partial	633	(58.8%)	577	(68.1%)	
None	46	(4.3%)	165	(19.5%)	
Hospitalized at presentation	1141	(19.3%)	185	(21.8%)	P=0.073
Dysentery at presentation[x]	1375	(23.3%)	105	(12.4%)	
≥1 IMCI general danger sign	3426	(57.9%)	590	(69.7%)	**P<0.0001**
Presented with at least 1 co-morbidity[xi]	1911	(32.3%)	360	(42.5%)	**P<0.0001**
Pneumonia	390	(6.6%)	82	(9.7%)	**P=0.001**
Malaria	1395	(23.6%)	219	(25.9%)	P=0.134
Malnutrition	305	(5.2%)	109	(12.9%)	**P<0.0001**
Other invasive bacterial infection	70	(1.2%)	17	(2.0%)	P=0.05
Upper respiratory tract infection	7	(0.1%)	0	(0%)	P=0.317

[ix] Flush toilet, ventilated improved pit latrine with or without water seal, or pour flush toilet not shared with other households

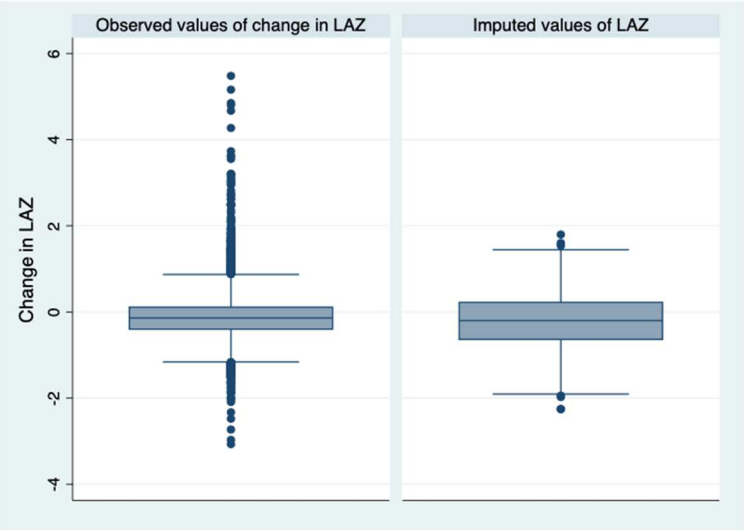
[x] Visible blood in stool observed by study staff or reported by caregiver at presentation; discharge diagnosis of dysentery per managing clinician upon leaving the healthcare facility; or observed in stool sample by laboratory staff

[xi] Per discharge diagnoses documented on medical records

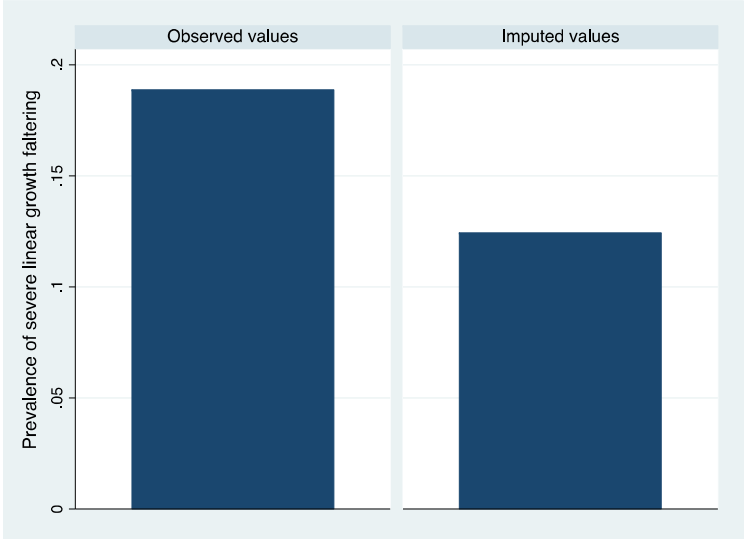
APPENDIX

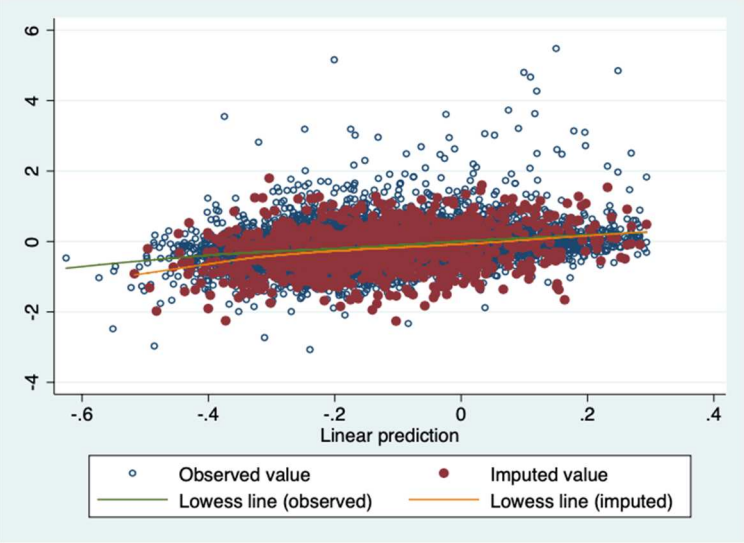
Additional File 1 Figure 1. Distribution of observed vs imputed outcome values

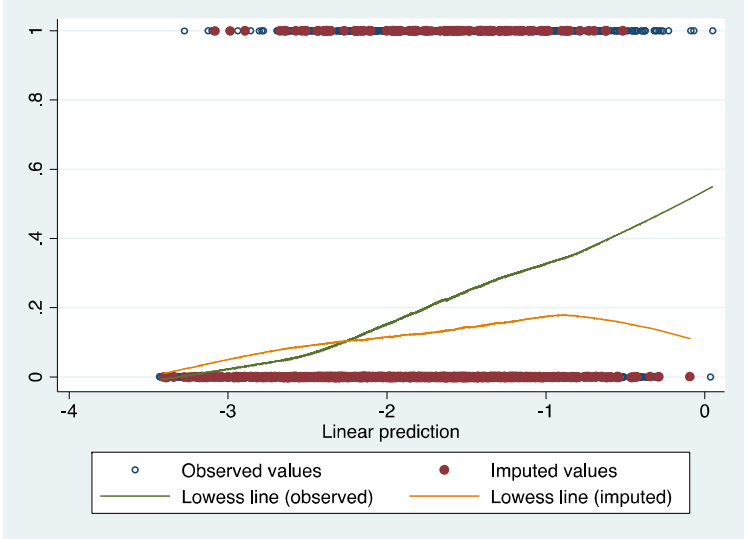
a. Change in LAZ



b. Prevalence of severe linear growth faltering (loss of ≥1 LAZ)







Additional File 1 Table 2. Risk factors for linear growth faltering among children 0-23 months old with MSD including imputed outcome data. Statistically significant results (p <0.05) are bolded.

	Severe linear growth faltering				Change in LAZ			
	n[xii]	%	Crude relative risks	Adjusted for age, site, and baseline LAZ	mean	SD	Crude difference in change in LAZ	Adjusted for age, site, and baseline LAZ
Age								
0-6 mo	386	31.5%	**2.10 (1.82, 2.43)**	**1.86 (1.61, 2.17)**	-0.24	0.72	**-0.14 (-0.17, -0.10)**	**-0.08 (-0.11, -0.05)**
>6-12 mo	726	27.6%	**1.85 (1.64, 2.08)**	**1.65 (1.46, 1.86)**	-0.23	0.55	**-0.13 (-0.16, -0.10)**	**-0.08 (-0.12, -0.04)**
>12-23 mo	437	15.1%	Reference	Reference	-0.11	0.47	Reference	Reference
Sex								
Male	924	18.8%	Reference	Reference	-0.18	0.52	Reference	Reference
Female	650	17.1%	0.93 (0.84, 1.03)	0.91 (0.82, 1.01)	-0.18	0.59	-0.01 (-0.03, 0.02)	0.01 (-0.02, 0.04)
Stunting								
No	1305	25.9%	Reference	Reference	-0.23	0.52	Reference	Reference
Yes	244	14.3%	**0.54 (0.46, 0.64)**	**0.59 (0.50, 0.70)**	-0.03	0.63	**0.21 (0.18, 0.25)**	**0.20 (0.17, 0.23)**
Wasting								
No	1155	22.2%	Reference	Reference	-0.15	0.56	Reference	Reference
Yes	394	26.3%	**1.23 (1.09, 1.39)**	**1.33 (1.17, 1.51)**	-0.28	0.53	**-0.12 (-0.15, -0.08)**	**-0.20 (-0.24, -0.17)**
MUAC (among >6 mos)								
≥12.5	945	20.9%	Reference	Reference	-0.16	0.51	Reference	Reference
<12.5 cm	218	22.4%	1.11 (0.95, 1.30)	**1.35 (1.14, 1.60)**	-0.21	0.51	-0.03 (-0.07, 0.01)	**-0.12 (-0.16, -0.08)**
Current breastfeeding (among < 6 mos)								
Exclusive	152	29.3%	Reference	Reference	-0.27	0.76	Reference	Reference
Partial	315	30.1%	1.01 (0.82, 1.25)	1.08 (0.85, 1.38)	-0.22	0.69	0.04 (-0.04, 0.11)	0.01 (-0.07, 0.10)
None	26	32.1%	1.17 (0.76, 1.81)	1.40 (0.89, 2.21)	-0.28	0.72	-0.09 (-0.25, 0.16)	-0.09 (-0.25, 0.16)
Diarrhea type[xiii]								
Acute	682	22.5%	Reference	Reference	-0.17	0.50	Reference	Reference
Prolonged	468	25.1%	1.13 (1.00, 1.27)	1.05 (0.92, 118)	-0.19	0.54	-0.01 (-0.04, -0.02)	-0.004 (-0.03, 0.03)
Persistent	155	24.1%	1.08 (0.90, 128)	0.98 (0.82, 1.18)	-0.15	0.59	0.02 (-0.03, 0.07)	0.03 (-0.02, 0.08)
Hospitalized at enrollment								
No	1213	21.9%	Reference	Reference	-0.17	0.55	Reference	Reference
Yes	336	28.0%	**1.31 (1.13, 1.50)**	**1.33 (1.15, 1.55)**	-0.22	0.60	-0.04 (-0.07, 0.002)	**-0.07 (-0.11, -0.03)**
Presentation with fever								
No	1213	21.8%	Reference	Reference	-0.17	0.55	Reference	Reference
Yes	335	29.2%	**1.34 (1.18, 1.52)**	**1.32 (1.16, 1.50)**	-0.25	0.57	**-0.08 (-0.12, -0.04)**	**-0.09 (-0.12, -0.05)**
Presentation with dysentery								

No	1229	23.3%	Reference	Reference	-0.19	0.56	Reference	Reference
Yes	320	21.6%	0.91 (0.80, 1.04)	0.86 (0.73, 1.02)	-0.14	0.54	**0.04 (0.01, 0.07)**	**0.07 (0.03, 0.11)**
Co-morbidities								
None	980	21.8%	Reference	*Reference*	-0.17	0.56	Reference	Reference
Any	569	25.2%	**1.18 (1.06, 1.31)**	**1.20 (1.04, 1.38)**	-0.20	0.55	**-0.03 (-0.07, -0.01)**	**-0.08 (-0.12, -0.04)**
Pneumonia	100	21.4%	0.95 (0.76, 1.19)	0.91 (0.73, 1.14))	-0.21	0.56	-0.01 (-0.06, 0.05)	-0.03 (-0.09, 0.03)
Malaria	428	26.9%	**1.22 (1.09, 1.37)**	**1.18 (1.01, 1.37)**	-0.20	0.56	-0.03 (-0.06, 0.002)	-0.03 (-0.07, 0.01)
Malnutrition	87	21.3%	1.04 (0.80, 1.36)	**1.44 (1.09, 1.90)**	-0.24	0.51	-0.06 (-0.12, 0.01)	**-0.21 (-0.27, -0.14)**
Other bacterial infection	30	35.3%	1.52 (1.05, 2.23)	(1.25 0.86, 1.83)	-0.24	0.60	-0.07 (-0.20, 0.07)	-0.04 (-0.17, 0.09)
Upper respiratory tract infection	1	14.3%	0.60 (0.08, 4.25)	0.54 (0.08, 3.84))	-0.11	0.61	0.07 (-0.34, 0.48)	0.09 (-0.31, 0.49)
IMCI danger signs								
None	539	19.7%	Reference	Reference	-0.15	0.54	Reference	*Reference*
At least 1	1010	25.4%	**1.33 (1.18, 1.50)**	**1.33 (1.18, 1.50)**	-0.21	0.56	**-0.05 (-0.08, -0.03)**	**-0.06 (-0.09, -0.03)**
3 signs present	19	22.9%	1.23 (0.69, 2.20)	1.27 (0.72, 2.26)	-0.28	0.76	-0.03 (-0.18, 0.12)	-0.04 (-0.18, 0.11)
2 signs present	320	25.8%	**1.36 (1.18, 1.58)**	**1.28 (1.10, 1.48)**	-0.21	0.58	**-0.06 (-0.10, -0.02)**	**-0.06 (-0.10, -0.02)**
1 sign present	670	25.3%	**1.32 (1.15, 1.51)**	**1.33 (1.16, 1.53)**	-0.20	0.55	**-0.05 (-0.08, -0.02)**	**-0.06 (-0.09, -0.02)**
Access to improved water								
No	857	23.1%	Reference	Reference	-0.18	0.57	Reference	Reference
Yes	692	23.0%	0.99 (0.97, 1.02)	1.04 (0.90, 1.21)	-0.19	0.54	-0.01 (-0.04, 0.02)	-0.03 (-0.07, 0.01)
Improved defecation facility								
No	1260	23.2%	Reference	Reference	-0.18	0.56	Reference	Reference
Yes	289	22.5%	0.96 (0.83, 1.11)	0.89 (0.74, 1.06)	-0.17	0.55	0.02 (-0.02, 0.06)	**0.06 (0.02, 0.11)**
Wealth index								
Lowest quintile	306	22.3%	Reference	Reference	-0.19	0.54	Reference	Reference
Second lowest	357	25.1%	1.12 (0.95, 1.32)	1.09 (0.93, 1.28)	-0.21	0.59	-0.02 (-0.06, 0.03)	-0.01 (-0.06, 0.03)
Middle	311	22.8%	1.02 (0.87, 1.20)	0.99 (0.84, 1.17)	-0.18	0.54	0.01 (-0.02, 0.06)	0.03 (-0.01, 0.07)
Second highest	272	21.3%	0.94 (0.79, 1.11)	0.94 (0.79, 1.12)	-0.17	0.53	0.02 (-0.02, 0.07)	0.04 (-0.003, 0.09)
Highest quintile	300	22.9%	1.01 (0.85, 1.20)	0.91 (0.77, 1.09)	-0.14	0.60	**0.05 (0.01, 0.10)**	**0.10 (0.05, 0.14)**

[xii] Indicates number with severe linear growth faltering

[xiii] Data on duration of diarrhea for the 7 days before enrollment were ascertained at enrollment (children with diarrhea lasting longer than 7 days were excluded at this point), and data on diarrhea duration for the 14 days following enrollment were ascertained with a memory aid suitable for groups of all literacy levels, which the caregiver returned at the 60-day follow up visit

CHAPTER 2

Effects of antibiotic exposure during moderate-to-severe diarrhea on linear growth faltering in children in the Global Enteric Multicenter Study

ABSTRACT

Background

Children with moderate-to-severe diarrhea (MSD) in resource-limited settings are at risk for linear growth faltering but it is unclear whether antibiotics during MSD protect against linear growth declines.

Methods

Using data on children aged 0-59 months presenting with MSD in the Global Enteric Multicenter Study (GEMS), we used linear and logistic regression to estimate associations of antibiotic exposure (prescription or administration at MSD presentation) with change in length-for-age z-score (ΔLAZ) and severe linear growth faltering (loss of ≥0·5 LAZ) between presentation and 50-90 days thereafter. We constructed propensity scores to adjust for exposure likelihood, and presented results overall and in pre-specified subgroups.

Findings

Among 7632 children with enrollment and follow-up LAZ data, mean age was 17·1 months and 81·3% were exposed to an antibiotic at presentation. Mean ΔLAZ was -0·20 and 22·8% lost ≥0·5 LAZ. Children who were antibiotic exposed were more likely to be hospitalized, and to present with a comorbidity, fever, or dysentery. After propensity score adjustment, antibiotic-exposed children lost 0·04 less LAZ than unexposed (95% confidence interval [CI]: 0·01, 0·07), and were 20% less likely to experience severe linear growth faltering (adjusted odds ratio: 0·80 [95% CI: 0·69, 0·94]). The effect size was larger among children with bacterial pathogen or acute malnutrition at presentation.

Interpretation

Antibiotics may attenuate the association of MSD with linear growth faltering in high-risk children, potentially through treating enteric bacterial pathogens. Any decisions regarding antibiotic management of MSD must consider antibiotic resistance.

INTRODUCTION

World Health Organization (WHO) guidelines for management of acute childhood diarrhea indicate that children should be rehydrated and provided with zinc. In addition, children with complicated severe acute malnutrition, dysentery or suspected cholera should receive antibiotics.[76] Implementation of these guidelines have contributed to substantial declines in child mortality due to diarrheal disease.[2] However, global incidence of diarrheal illness has remained relatively stable[77] and diarrhea episodes that do not lead to death can cause linear growth deterioration.[7,8] Linear growth faltering can lead to stunting, which is associated with health and cognitive detriments.[11] Interrupting the association between diarrheal illness and linear growth faltering may improve long-term outcomes in children.

Little is known about the effectiveness of diarrhea management strategies for preserving linear growth following diarrheal episodes. Antibiotics have shown some growth-promoting effects in children living in resource-limited settings.[14] Antibiotics may preserve linear growth by treating bacterial etiologies of diarrhea, or subclinical bacterial enteric infections that lead to environmental enteric dysfunction (EED), a syndrome thought play a putative role in childhood stunting. Finally, some antibiotics have immune-modulatory effects that address gut or systemic inflammation caused by EED or other chronic infections. However, the effects of antibiotics during diarrhea on child linear growth are undefined.

Using previously collected data from the Global Enteric Multicenter Study (GEMS)[7], we conducted a retrospective cohort analysis to estimate the effects of antibiotics, accounting for likelihood of antibiotic exposure based on clinical and sociodemographic factors, during moderate-to-severe diarrhea (MSD) on linear growth in the 50-90 days following the episode, among children 0-59 months presenting with MSD to health facilities in seven low- and middle-income countries (LMICs). We also conducted *a priori* exploratory analyses to evaluate the effect in subgroups by site, acute malnutrition status, age category, or type of pathogen detected.

METHODS

Study setting and design

This secondary analysis is a case-only analysis in GEMS-1[7], a prospective case-control study of diarrhea etiology conducted between 2007 and 2011 in Bangladesh, India, Pakistan, Kenya, Mali, Mozambique, and The Gambia. MSD cases were children 0-59 months old seeking care at study health facilities for an episode of new, acute diarrhea (≥3 abnormally loose stools in the last 24 hours with an onset in the prior 7 days following ≥7 diarrhea-free days) and dehydration (sunken eyes, loss of skin turgor, or intravenous hydration administered or prescribed), dysentery (presence of visible blood in diarrhea), or admission to hospital. The study team performed physical exams and conducted interviews with caregivers at enrollment and at a follow up visit 50-90 days after enrollment to ascertain clinical, anthropometric, and sociodemographic factors. Child's weight and mid-upper arm circumference (MUAC) were measured at enrollment (diarrhea presentation), and height/length were measured thrice at each visit. Stool samples were obtained at presentation, and assessed for a panel of more than 40 putative pathogens. This analysis is confined to putative bacterial pathogens detected using conventional culture techniques (*Aeromonas* species [spp.], *Campylobacter* spp., *Salmonella* spp., *Shigella* spp, or *Vibrio cholerae*). Three putative *Escherichia coli* colonies from every stool were pooled and analyzed by multiplex PCR to detect targets for enterotoxigenic (ETEC), enteropathogenic (EPEC), enteroinvasive, enterohemorrhagic, and enteroaggregative E. coli. Further details on the GEMS study procedures and laboratory testing have been described elsewhere.[7,78,79]

MSD cases were included in this analysis if both enrollment and follow-up length-for-age z-score (LAZ) measurements were available. We also excluded children with implausible length/LAZ values, defined as enrollment or follow up LAZ > 6 or < -6 and change in (Δ) LAZ > 3; a length gain of > 8 cm for follow up periods 49-60 days and >10 cm for periods 61-91 days among infants ≤ 6 months, a length gain of > 4 cm for follow up periods 49-60 days and >6 cm for periods 61-91 days among children > 6 months, or length values that were >1·5 cm lower at follow up than at enrollment.

Outcome, exposure, and sub-group definitions

Linear growth faltering was defined as (1) ΔLAZ between enrollment and follow up with ΔLAZ<0 representing a loss, and (2) severe linear growth faltering (loss of ≥0.5 LAZ). Antibiotic exposure was defined as any antibiotic prescribed or administered in the health center per medical records at MSD presentation. For the purpose of this analysis, metronidazole was classified as an antibiotic. Definitions of select covariates are given in Supplementary Material Table 1.

We conducted exploratory analyses examining the effect within *a priori* subgroups. We examined the effect of antibiotics among children with one or more bacterial pathogens detected in two categorizations: 1) among children with any potential enteric bacterial pathogen detected (enteropathogenic *Escherichia coli* [EPEC], enterotoxigenic [ETEC], enteroaggregative *E. coli* [EAEC], *Aeromonas* species (spp.), *Campylobacter* spp., *Salmonella* spp., *Shigella* spp, or *Vibrio* cholerae) and 2) among children with a bacterial pathogen associated with MSD in GEMS (bacteria with the top 10 attributable fractions in any age category, all sites combined: *Shigella* spp., heat-stable toxin ETEC, *Campylobacter jejuni*, typical EPEC, *Aeromonas* spp., *Vibrio cholerae*, or non-typhoidal *Salmonella* [NTS])[7]. We also assessed the effect by wasting status at presentation (weight-for-length z-score [WLZ] < -2, or middle upper arm circumference [MUAC] < 12.5 cm among children 6-59 months old), by age (0-11, 12-23, 24-59 months), and by site.

Statistical analysis

In this assessment of a non-randomized treatment, we expected children's likelihood of being exposed to an antibiotic to be based, in part, on factors that were also associated with linear growth faltering. We constructed propensity scores to adjust for factors that were imbalanced between children who were exposed to antibiotic versus not to mitigate this bias. We considered a variable to be imbalanced based on a standardized difference of ≥ 0·1 or ≤ -0·1 between treated and untreated groups.[80] Clinical and sociodemographic factors collected at MSD presentation were included in the propensity score if: (1) they were imbalanced between children who were and were not antibiotic exposed, or (2) if they were associated with linear growth in prior research, irrespective of imbalance.[81] Study site was considered a confounder due to the variability in antibiotic use by site and was included in the propensity scores. Baseline LAZ was also adjusted for by inclusion in the propensity scores. Any variable that remained imbalanced after propensity score adjustment were included in the regression model as a covariate[82]. Models were also adjusted for follow up time.

We assessed overlap of propensity score values by visually inspecting scatter plots of propensity score values in children by antibiotic exposure status. We excluded children from the analysis if their propensity score values had insufficient overlap to ensure a robust comparison of outcomes.[80] To evaluate goodness-of-fit of the propensity scores, we used standardized differences to assess covariate balance between exposed and unexposed children in the cohort overall, and within each of the sub-group strata to assess potential for bias in sub-group analyses.

Calculations of standardized differences were done in Microsoft Excel, and all other analyses were conducted in Stata SE 14. We used linear regression models to estimate difference in ΔLAZ

and 95% confidence intervals (95% CIs) associated with antibiotic exposure, and logistic regression models to estimate adjusted odds ratios (aORs) of severe linear growth faltering with 95% CIs. We used post-estimation risk calculation tools to estimate adjusted number-needed-to-treat (NNT) for the binary outcome of severe linear growth faltering.

We conducted a sensitivity analysis in which we restricted our definition of antibiotic exposure to only children who received an antibiotic in the health center per medical records (excluding those who received only a prescription), and an analysis evaluating the effects of specific antibiotics which were commonly used in GEMS and which may have action against common enteric bacterial pathogens (ciprofloxacin and cotrimoxazole). We also repeated the main analysis using imputed outcomes for those missing follow up LAZ. We conducted sed multiple imputations for monotone missing data, specifying linear regression models to impute ΔLAZ and logistic regression to impute severe linear growth faltering based on baseline characteristics associated with missingness. Finally, we conducted rule-out sensitivity analyses to identify the strength of association between an unmeasured confounder and the outcome at which the main effect would be null.[83] While this assessment of a single binary confounder cannot evaluate the joint effects of several unmeasured factors, this sensitivity analysis provides a general evaluation of robustness of results to unmeasured confounding.

RESULTS

Of the 9,439 MSD cases in GEMS, 1,294 children were excluded for missing or implausible LAZ measurements. Of the 8,145 children eligible for the analysis, an additional 513 were excluded for missing data on covariates included in the propensity score or inadequate overlap in propensity score values, resulting in 7,632 children in the analysis.(Figure 1) Outcomes were imputed for an additional 1051 children, resulting in 8671 children in the analysis including imputed outcomes (Supplementary Material Figure 1a/1b). Median duration of follow up was 63 days with an interquartile range of 59 to 70 days (Supplementary material Figure 2).

Of the 7,632 children included in the analysis, 81·3% (n=6,201) were given or prescribed an antibiotic at MSD presentation. Of these, 74·1% (n=4,592) only received a prescribed antibiotic, 8·1% were given the antibiotic in the health center, and 17·8% both received a prescription and were given an antibiotic in health center. The most commonly used antibiotics were cotrimoxazole (42·4% of the antibiotic exposed), and ciprofloxacin (33·1%) (Figure 2). cotrimoxazole use was more common at the African sites, and ciprofloxacin at the Asian sites.

Mean age was 17·1 months (standard deviation = 12·3) and 43·5% were female (Table 1). Children who were given/prescribed antibiotics were more likely to be hospitalized at presentation, more likely to be diagnosed with at least one co-morbidity (including malaria or pneumonia), and more likely to present with fever or dysentery. Children who were given/prescribed antibiotics were also older and more likely to be in an upper wealth quintile, but less likely to have access to improved defecation facilities and less likely to have a primary caregiver with education higher than primary school. The propensity scores resulted in ideal balance for all but one covariate, study site (Figure 3a), which was thus adjusted for in the regression models as a covariate. Propensity score values overlapped sufficiently between treated and untreated children for all values ≥ 0.2 (Figure 3b).

Mean, unadjusted ΔLAZ among children included in the analysis was -0·20 LAZ between MSD presentation and follow up 50-90 days later. Approximately 22·8% (n=1740) lost ≥0·5 LAZ, and LAZ declined by ≥1 in 4·8% (n=367) during the study period. Without propensity score adjustment, there was no association between receiving antibiotics and linear growth faltering (difference in

ΔLAZ [β]: 0·01 [95% CI: -0·01, 0·04]; OR of severe linear growth faltering: 0·90 [95% CI: 0·79, 1·03]). After adjustment for propensity score, site, and follow up time, children who were exposed to antibiotics lost 0·04 LAZ less (adjusted β [aβ]: 0·04 [95% CI: 0·01, 0·07]), and were 20% less likely to experience severe linear growth faltering (aOR: 0·80 [95% CI: 0·69, 0·94]) than children who were not exposed to antibiotics (Table 2). Twenty-eight children would need to be treated with antibiotics to prevent one case of severe linear growth faltering (95% CI: 16, 111). An unmeasured confounder would need at least a 1·6-fold association with the outcome to nullify the effect (Supplementary Material Table 2).

When restricting the antibiotic exposure definition to only children who received an antibiotic in the health center (n=1870), children who received an antibiotic lost 0·03 less LAZ (95% CI -0·03, 0·10), and had 19% lower odds of severe linear growth faltering (aOR: 0·81 [95% CI: 0·58, 1·12]) than those who did not receive any antibiotic Results were not statistically significant for either outcome, possibly due to much lower statistical power. The analysis including imputed outcome values (n=8671) yielded similar results to the primary analysis (aβ: 0·04 [95% CI: 0·005, 0·08]; aOR: 0·85 [95% CI: 0·74, 0·98]). Children exposed to cotrimoxazole lost 0·035 less LAZ (95% CI: 0·002, 0·07) and had 21% lower odds of severe linear growth faltering (aOR: 0·79 [95% CI: 0·66, 0·95]) than those who were exposed to no antibiotic. Compared to children who did not were exposed to any antibiotic, children who were exposed to ciprofloxacin lost 0·08 less LAZ (95% CI: 0·05, 0·12) and had 37% lower odds of severe linear growth faltering (aOR: 0·63 [95% CI: 0·52, 0·77]).

The effects appeared more pronounced in children who were acutely malnourished and those in whom a pathogenic bacteria were identified (Figure 4). Antibiotic exposure was associated with 0·12 LAZ less loss (95% CI: 0·06, 0·18) among children with WLZ < -2 at MSD presentation, and with 0·09 LAZ less loss (95% CI: 0·01, 0·17) among 6-59 months old with MUAC < 12·5 cm. Similarly, among children with acute malnutrition by either metric, those who were exposed to antibiotics had approximately half the odds of severe linear growth faltering than those who did were not. The effects of antibiotics was stronger in children in whom a bacterial pathogen was detected at presentation ($a\beta_{\text{any bacteria}}$: 0·06 [95% CI: 0·02, 0·10]; $a\beta_{\text{diarrhea-associated bacteria}}$: 0·08 [95% CI: 0·03, 0·13]) Antibiotics were associated with 33% lower odds of severe linear growth faltering (aOR: 0·67 [95% CI: 0·52, 0·86]) among children with a diarrhea-associated bacterial pathogen. Trends by age and site were less clear. A larger effect size was observed among 12-23 month old children, but there were not enough outcomes in the 23-59 month category to calculate an OR. The effects of antibiotics on ΔLAZ and on severe linear growth faltering varied considerably by site. Covariate balance was generally good within strata, but covariate balance was not achieved at all sites (Supplementary Material Figures 4-6).

DISCUSSION

Substantial losses in LAZ have been reported in children presenting with MSD in LMICs.[7] In this secondary analysis of children enrolled in GEMS1, children who were given or prescribed an antibiotic at presentation with MSD lost less LAZ and were less likely to have severe linear growth faltering than children who were not exposed to antibiotics.

This effect emerged after accounting for likelihood of receiving antibiotics based on clinical and host factors. We found that children who were given or prescribed an antibiotic tended to have more severe disease, and differed in sociodemographic and anthropometric characteristics, than children who were not given/prescribed an antibiotic. Observational analyses of the effects of antibiotics on clinical outcomes among children with diarrhea should consider adjustment for factors associated with likelihood of receiving antibiotics.

Other research has documented the growth-promoting effects of antibiotics. It is well-established that antibiotic additives to animal feed promotes growth in livestock[84], particularly among animals exposed to fecal contamination in early life.[85] This suggests antibiotics may promote growth through directly treating micro-organisms detrimental to the growth of the host. In our study population of children 0-59 months old in LMICs, we observed the effect of antibiotics on linear growth was stronger among children whose MSD was associated with known bacterial pathogens that generally respond to the most common antibiotics used, ciprofloxacin and cotrimoxazole. This strengthens the hypothesis that antibiotics may be acting directly by treating clinical or subclinical bacterial infections. Further, we noted a stronger effect associated with ciprofloxacin, the WHO-recommended first-line treatment for *Shigella*-associated diarrhea[86], and the effect to be stronger in age groups with the higher prevalences of *Shigella* infection.[7] Shigella and other pathogenic enteric bacteria have been reported to be associated with linear growth faltering in children. The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health (Mal-ED) study reported an increased risk of linear growth deficits associated with specific bacterial pathogens, including *Shigella* spp., *Campylobacter* spp., tEPEC, and enteroaggregative *E. coli.*[87,88] A study among Bangladeshi infants reported that diarrhea attributed to *Campylobacter jejuni/coli* or *Shigella* spp./enteroinvasive *E. coli* was associated with linear growth faltering.[59]

Antibiotics may also influence linear growth indirectly by improving inflammation or gut function, perhaps through the treatment of EED. EED is highly prevalent among children in LMICs and is characterized by disruptions in the intestinal architecture resulting in increased intestinal permeability and nutrient malabsorption, dysbiosis and increased translocation of bacterial products into the systemic circulation.[69] Antibiotics treat EED through direct antimicrobial effects on specific pathogens, treatment of small intestine bacterial overgrowth (SIBO)[89,90] or anti-inflammatory action of certain antibiotics, such as azithromycin or cotrimoxazole. We reported a larger effect size in children who were acutely malnourished at MSD presentation, possibly explained by higher prevalence of pathogenic enteric bacteria [91,92], or higher prevalence of SIBO[93] in this population.

Early life antibiotic exposure has been reported to be associated with increases in childhood weight gain and body mass index in high-income countries[94] as well as children in resource-limited settings.[61] Improvements in linear and ponderal growth have been reported in a meta-analysis of 10 clinical trials of any oral antibiotic administered for any indication among children in LMICs. The authors reported an increase of 23·8 g/month [95% CI: 4·3, 43·3] and 0·04 cm/month [95% CI: 0·00, 0·07]) associated with antibiotics.[14] However, there is limited evidence available on the effectiveness of antibiotic treatment for promoting growth following diarrhea. A systematic review of clinical trials of diarrhea management interventions for reducing post-diarrhea adverse outcomes in children in LMICs reported that many trials of antibiotic management for diarrhea do not report any growth outcomes, and there is limited evidence for other interventions to reduce post-diarrhea growth faltering.[95] The modest protective effect of antibiotics against linear growth faltering that we observed in GEMS is consistent with findings from the MAL-ED study, which reported found diarrheal episodes unaccompanied by antibiotic treatment to be the only diarrhea associated with growth (albeit modestly).[96] However, robust clinical trial evidence will be needed for a more definitive answer to the question of growth-promoting effects among children with diarrhea, and to inform diarrhea management decisions.

While this analysis suggests that antibiotic management of MSD may confer modest protection against linear growth faltering, the public health benefit remains unclear. We reported that 28 children with MSD would need to be treated with antibiotics in order to prevent one case of severe

linear growth faltering (loss of ≥ 0·5 LAZ). It is unclear whether this magnitude of effect would lead to clinically meaningful reductions in stunting-associated morbidity and mortality. In addition, any potential benefits resulting from improvements in LAZ must be cautiously weighed against the individual and community-wide risk of increasing antibiotic resistance as well as side-effects and costs associated with antibiotic treatment.

Strengths of our analyses include the large sample size, multi-country setting, rigorous data collection practices of GEMS, and use of propensity scores to account for potential confounding by indication. There are limitations as well. First, this is an observational study and causal inference must be interpreted with caution. A limitation that affects all propensity score analyses is the possibility of residual bias due to unmeasured confounding. There also may have been misclassification of antibiotic exposure, as the majority of children considered antibiotic exposed received only a prescription for antibiotics, with no confirmation of whether the child actually took the antibiotic. Data on antibiotic use during follow up beyond what was prescribed for the index illness were also not available. The largest effect size was seen among the sickest and most malnourished children who were more likely to be hospitalized and it cannot be determined with certainty whether nutritional rehabilitation was provided. Misclassification of wasting status was likely, as children's weights were likely affected by dehydration. Misclassification of pathogen categories is also possible. Because bacterial enteropathogens can be carried asymptomatically, it cannot be ascertained whether those identified in a child's stool sample were pathogenic by causing diarrhea, intestinal injury, or another mechanism and whether growth was directly related to the termination of these harmful processes. GEMS data have been since re-analyzed using quantitative methods, but the current analysis used pathogen results from conventional laboratory methods. However, these misclassifications are expected to bias the result toward null findings, so if these biases are present, we would expect the true effect actually being stronger than what we report. The relatively short follow up window of 50-90 days also limited our ability to assess longer term impacts of antibiotics on growth and excluding children who died in the study period may have resulted in a survival bias. Finally, propensity scores were constructed to examine the overall effect, and covariate balance was not ideally achieved in all sub-group strata. In particular, we noted important differences in effect by age and site. While these inconsistencies may reflect covariate imbalance within strata, further research should evaluate possible age and setting-specific effects of antibiotic on growth.

CONCLUSION

Antibiotic use during an episode of MSD of bacterial origin appears to be associated with modest protection against linear growth faltering in children 0-59 months old in LMICs. Whether antibiotics are a useful intervention for reducing the negative impacts of diarrhea-associated growth faltering in a sub-set of high-risk children in these settings will depend on robust clinical trial evidence and careful consideration of the potential population risks and benefits to inform any modifications to existing treatment strategies for acute diarrhea in children in LMICs.

TABLES AND FIGURES

Figure 1. Flowcharts of included subjects

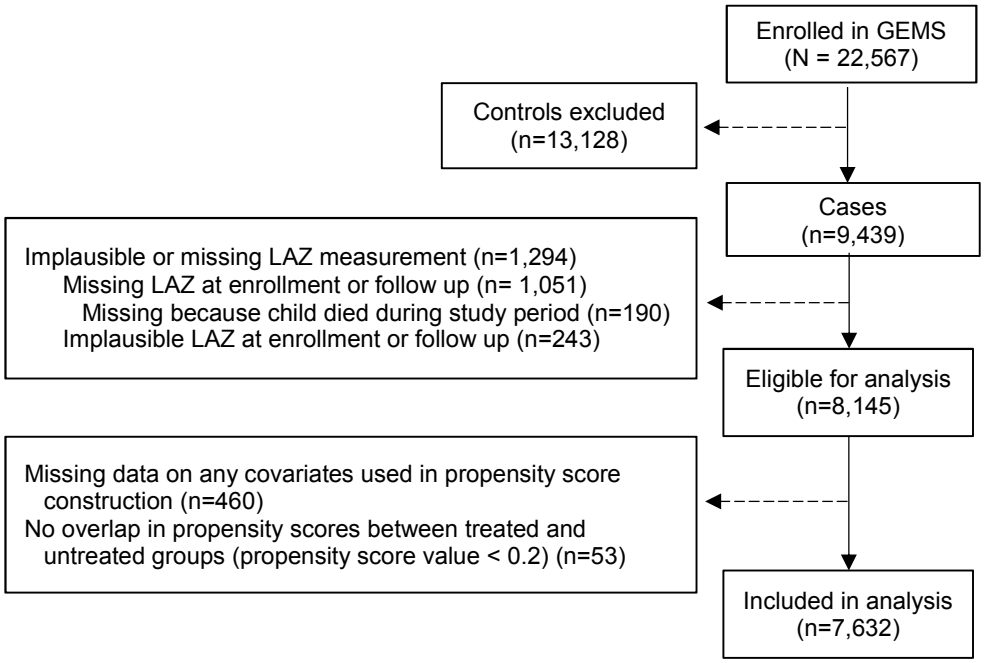
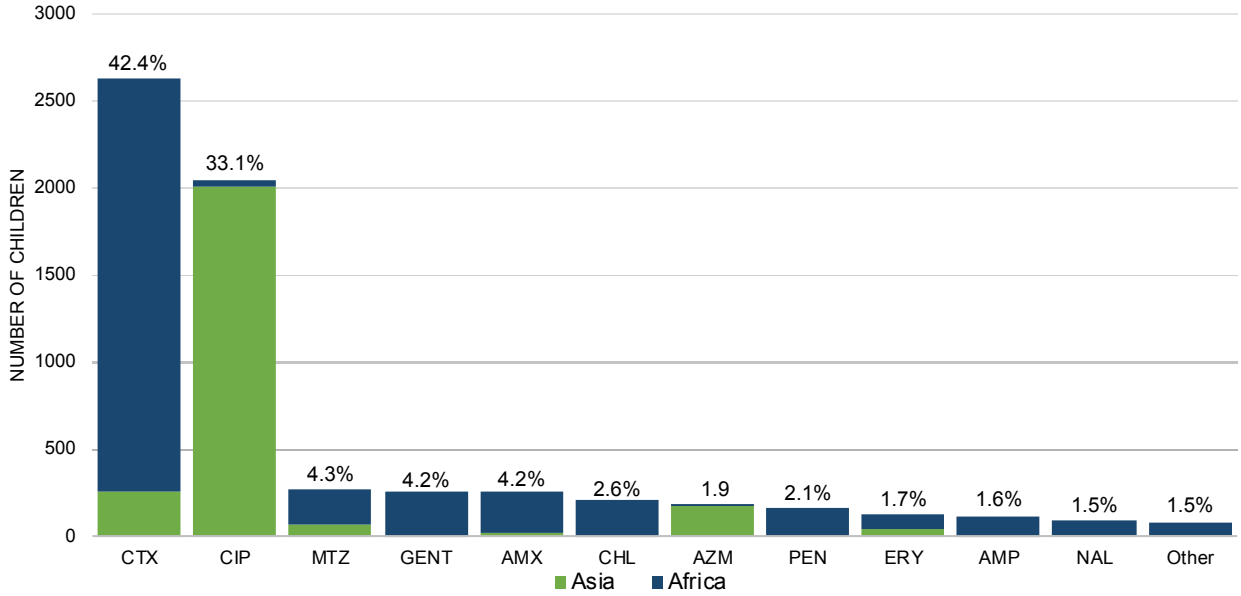


Figure 2. Antibiotics given or prescribed at MSD presentation by region



Abbreviations: CTX = cotrimoxazole, CIP = ciprofloxacin, MTZ = metronidazole, GENT = gentamycin, AMX = amoxicillin, CHL = chloramphenicol, AZM = azithromycin, PEN = penicillin, ERY = erythromycin, AMP = ampicillin, NAL = nalidixic acid

Note: Percentages are among the 6201 children who received an antibiotic.
"Other" includes ceftriaxone (n=21), pivmecillinam (n=5), other macrolides (n=3)

Table 1. Baseline characteristics of GEMS cases of moderate-to-severe diarrhea (MSD) cases who did and did not receive antibiotics at presentation in the GEMS study (2007-2011)

Abbreviations: SD= standard deviation, mo = months, LAZ = length-for-age z-score, MUAC = mid-upper arm circumference, WLZ = weight-for-length z-score, IMCI = Integrated Management of Childhood Illness

	No antibiotics N=1431 (18.6%)	Exposed to antibiotics N=6201 (81.3%)	p-value[xiv]
	N(%) Mean(SD)	N(%) Mean(SD)	
Sociodemographic factors			
Age	15.3 (11.9)	17.5 (12.4)	p<0.0001
0-11 mo	682 (47.7%)	2499 (40.3%)	
12-23 mo	469 (32.8%)	2122 (34.2%)	p<0.0001
24-59 mo	280 (19.6%)	1580 (25.5%)	
Female	628 (43.9%)	2675 (43.1%)	p=0.607
Exclusively breastfed (among 1335 children ≤ 6 mo)	144 (33.0%)	275 (27.8%)	p=0.007
Access to an improved defecation facility	495 (34.6%)	859 (13.9%)	p<0.0001
Upper wealth quintile	466 (32.6%)	2538 (40.9%)	p<0.0001
Wealth index	-0.1 (1.0)	0.0 (1.0)	p=0.005
Caregiver completed ≥ primary school	300 (21.0%)	978 (15.8%)	p<0.0001
Site			p<0.0001
the Gambia	144 (10.1%)	640 (10.3%)	
Mali	112 (7.8%)	1562 (25.2%)	
Mozambique	74 (5.2%)	357 (5.8%)	
Kenya	282 (19.7%)	988 (15.9%)	
India	103 (7.2%)	1280 (20.6%)	
Bangladesh	74 (5.2%)	1177 (19.0%)	
Pakistan	642 44.9%)	197 (3.2%)	
Clinical factors			
Axillary temperature ≥37.5 C	385 (26.9%)	1915 (30.9%)	p=0.003
Duration of diarrhea	6.8 (4.6)	6.5 (4.1)	p<0.0001
Presented with dysentery	116 (8.1%)	1854 (29.9%)	p<0.0001
Presented with dehydration	1348 (94.2%)	4817 (77.7%)	p<0.0001
Presented with any comorbidity[xv]	389 (27.2%)	2195 (35.4%)	p<0.0001
Malaria	306 (21.4%)	1643 (26.5%)	p<0.0001
Pneumonia	44 (3.1%)	445 (7.2%)	p<0.0001
Malnutrition	50 (3.5%)	332(5.4%)	p<0.0001
Presented with multiple comorbidities	19 (1.3%)	302 (4.9%)	p<0.0001
Presented with any IMCI danger sign[xvi]	895 (62.5%)	3514 (56.7%)	p<0.0001
Presented with multiple IMCI danger signs	323 (22.6%)	1085 (17.5%)	p<0.0001
Hospitalized at enrollment	182 (12.7%)	1218 (19.6%)	p<0.0001
Duration of hospitalization if hospitalized, days	3.2 (1.5)	3.2 (1.7)	p=0.764
Nutritional status			
Stunting at presentation (LAZ < -2)	473 33.1%)	1506 24.3%)	p<0.0001
Mean LAZ	-1.5 (1.3)	-1.2 (1.2)	p<0.0001
Wasting at presentation			
MUAC < 12.5 cm	351 (24.5%)	842 (13.58%)	p<0.0001
WLZ < -2	352 (24.6%)	1264 (20.4%)	p<0.0001
Mean MUAC	13.5 (1.5)	13.9 (1.4)	p<0.0001
Mean WLZ	-1.1 (1.2)	-1.0 (1.3)	p=0.063
Severe acute malnutrition at presentation (WLZ < -3)	116 (8.1%)	408 (6.6%)	p=0.012

[xiv] P-values for differences between exposure groups correspond to t-tests for continuous variables and χ^2 tests for categorical variables

[xv] Clinician diagnoses documented on medical records

[xvi] WHO Integrated Management of Childhood Illness general danger signs: convulsions, vomits everything, lethargic or unconscious, not able to drink or breastfeed

Figure 3a. Balance of covariates before and after propensity score adjustment

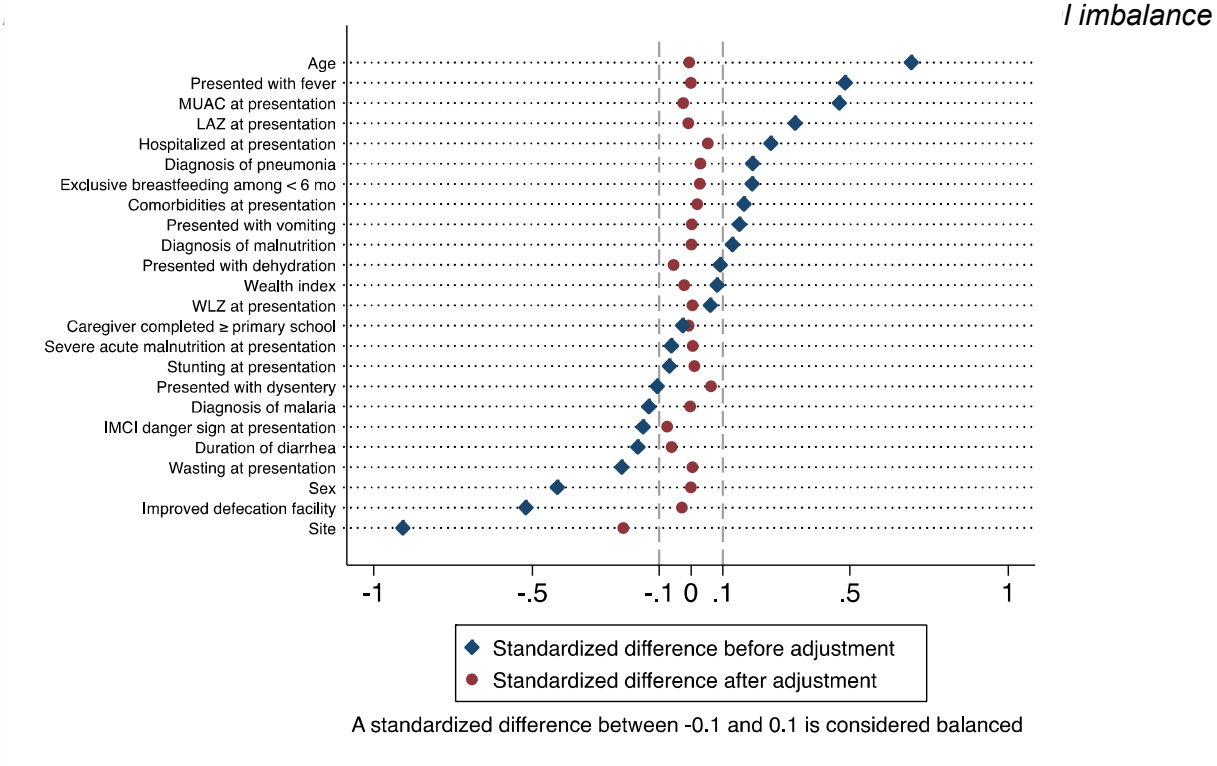


Figure 3b. Distributional overlap of propensity score values between treated and untreated children

Note: children with propensity scores < 0.2 were excluded due to inadequate overlap (n=53)

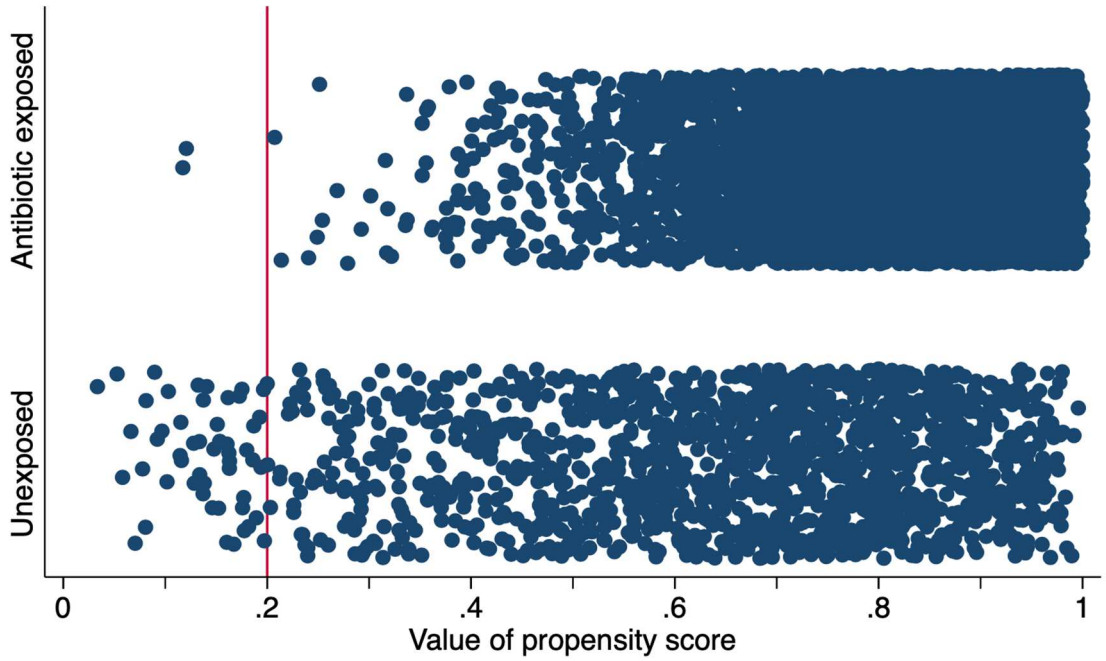


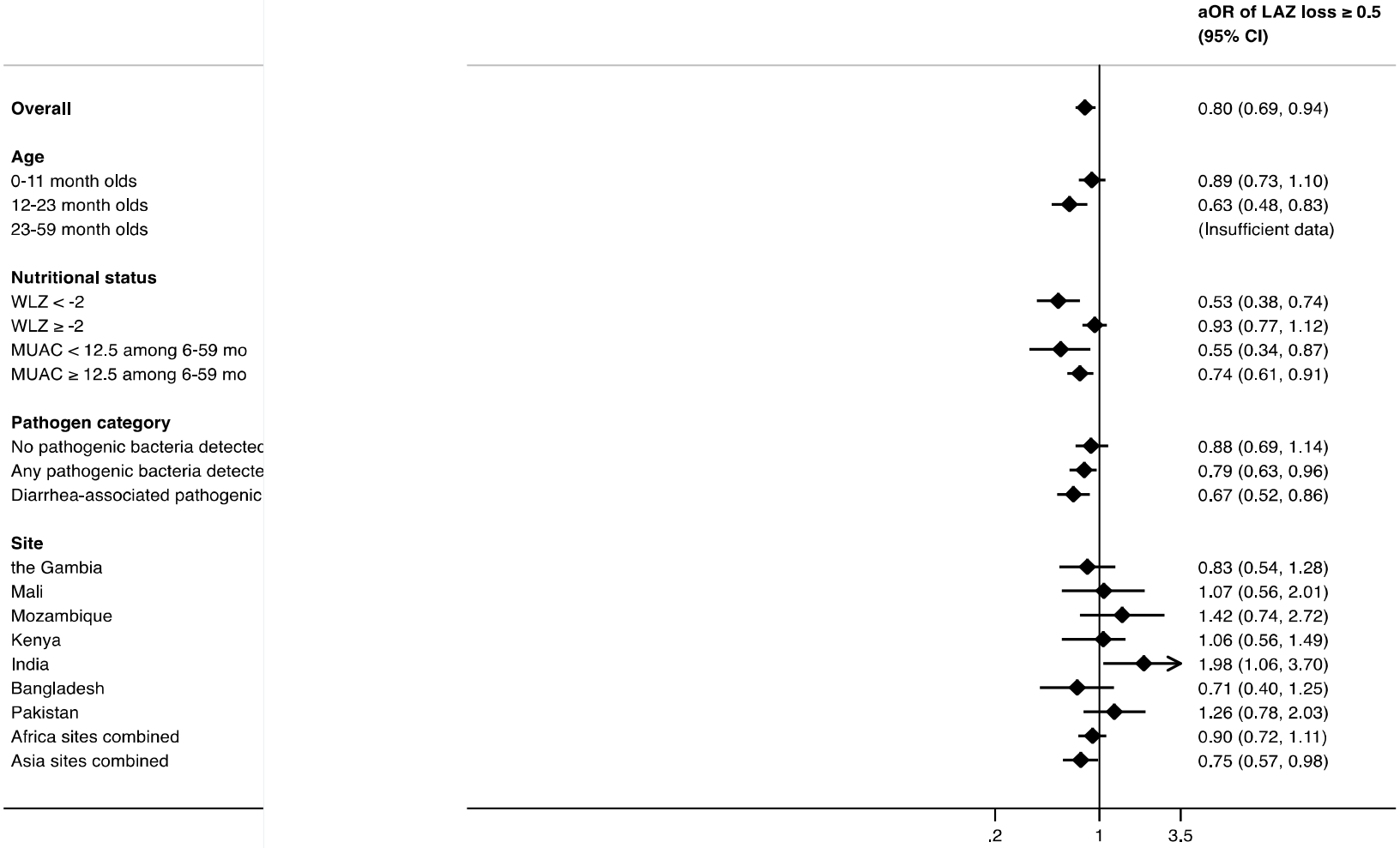
Table 2. Linear growth faltering by 50-90 days of follow-up among 7632 children presenting with MSD

	ΔLAZ		Loss of ≥0.5 LAZ			
	Adj. mean (SE)	Adj. difference (95%CI)	Adj. prevalence	aOR	(95% CI)	NNT (95% CI)
Exposed to antibiotics	-0.19 (0.01)	0.04 (0.01, 0.07)	22.1%	0.80	(0.69, 0.94)	28 (16, 111)
Unexposed	-0.23 (0.01)	--	25.7%		--	--

Models are adjusted for propensity score, site, and duration of follow up.
Abbreviations: NNT= number needed to treat; Adj. =adjusted; LAZ = length-for-age z-score; aOR = adjusted odds ratio; 95% CI= 95% confidence interval; SE = standard error

Figure 4. Effects of antibiotic exposure on linear growth faltering among children presenting with moderate-to-severe diarrhea, overall and within subgroups

Abbreviations: LAZ = length-for-age z-score, WLZ = weight-for-length z-score, MUAC = mid-upper arm circumference, aOR = adjusted odds ratio, 95% CI= 95% confidence interval



APPENDIX

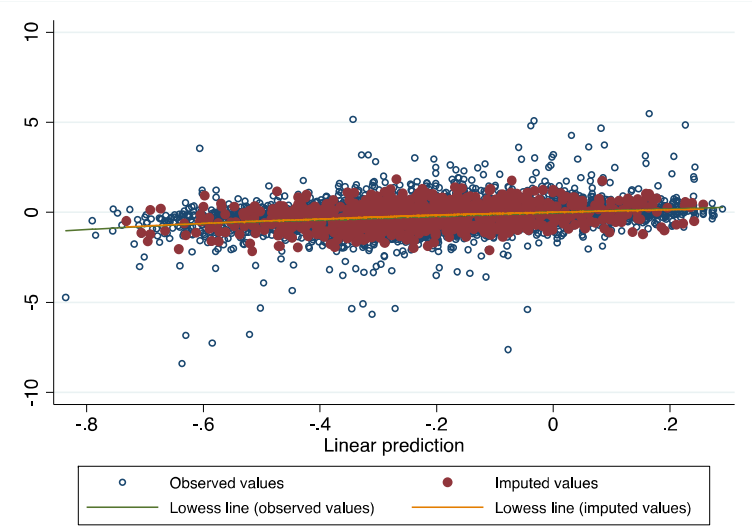
Table 1. Definitions of select covariates included in propensity score adjustment

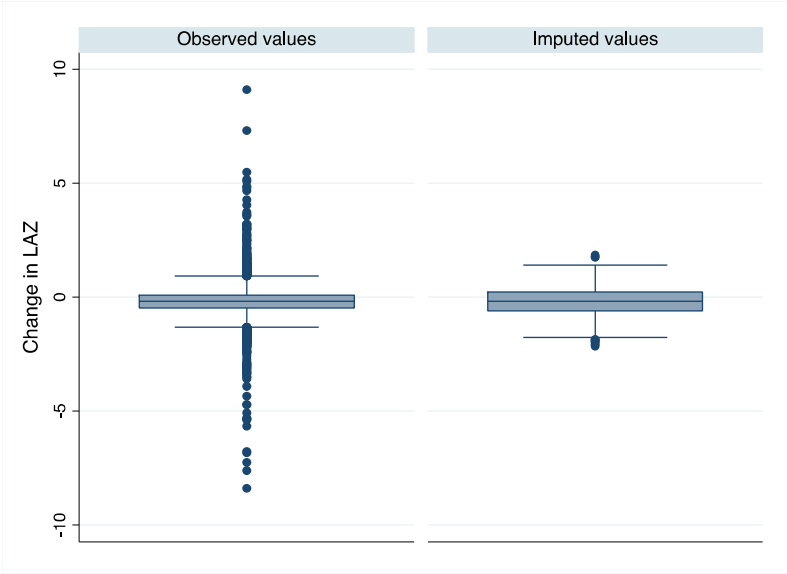
Covariate	Definition
Diagnoses of co-morbidities (including malaria, pneumonia, and malnutrition)	Final diagnosis per clinician impression as documented in medical records
WHO Integrated Management of Childhood Illness (IMCI) general danger sign	Documentation in medical records of at least one clinical characteristic that would be considered to be a WHO IMCI general danger sign: convulsions, unable to drink, lethargic or unconscious, vomiting
Length-for-age and weight-for-length z-score at presentation	Calculated according to WHO standards using WHO Stata macro code.[38]
Dysentery	Discharge diagnosis of dysentery per managing clinician upon leaving the healthcare facility or visible blood in stool observed by study staff or reported by caregiver at presentation, or observed in stool sample by laboratory staff
Duration of diarrhea	Duration of diarrhea was defined as the duration of diarrhea at presentation plus duration of diarrhea after enrollment. Duration of diarrhea for the 7 days before enrollment was ascertained at enrollment (children with diarrhea lasting longer than 7 days were excluded at this point) and diarrhea duration for the 14 days following enrollment was ascertained with a memory aid suitable for groups of all literacy levels which the caregiver returned at the 60-day follow up visit. Cessation of the enrollment episode was defined as two consecutive days in which diarrhea was not reported.
Access to improved defecation facility	Caregiver report of access to the following: flush toilet, ventilated improved pit latrine with or without water seal, or pour flush toilet not shared with other households
Wealth quintile	Quintile of a wealth effects score calculated from asset ownership information reported by caregiver at enrollment[39]

Note: Variables included in the propensity score due to imbalance between exposed and unexposed children included age, study site, breastfeeding history, MUAC at presentation, LAZ at presentation, hospitalization at presentation, caregiver education, duration of hospitalization (among those hospitalized), presentation with any or multiple comorbidities (including pneumonia, malaria, or other bacterial infection), vomiting, presence of any IMCI danger sign and number of danger signs, dehydration, duration of diarrhea, and dysentery. Variables included in the propensity score on the basis of their associations with linear growth faltering in prior analyses[97] included WLZ at presentation, sex, wealth index, unimproved defecation facility, and fever at presentation.

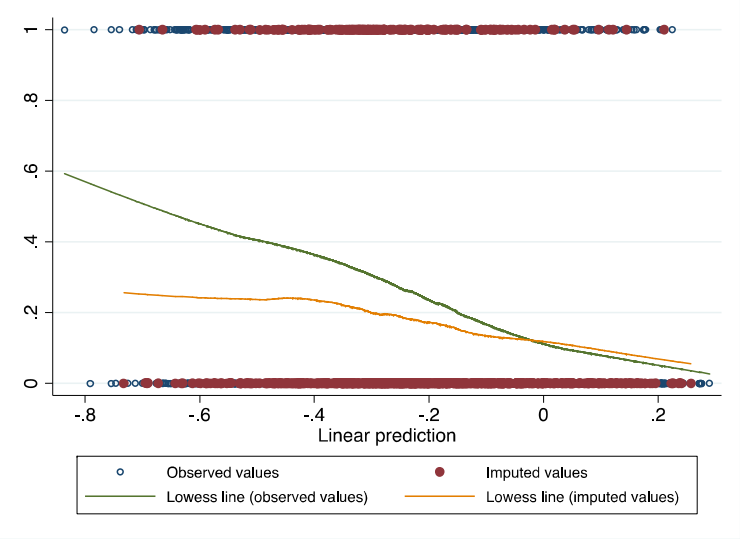
Figure 1. Distribution of observed verses imputed outcome values

a. Change in LAZ





b. Severe linear growth faltering



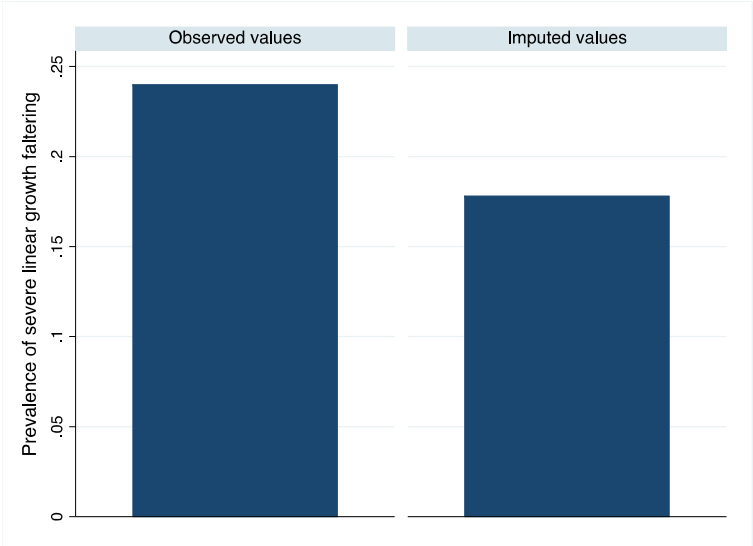


Figure 2. Distribution of follow up time of children included in this secondary analysis

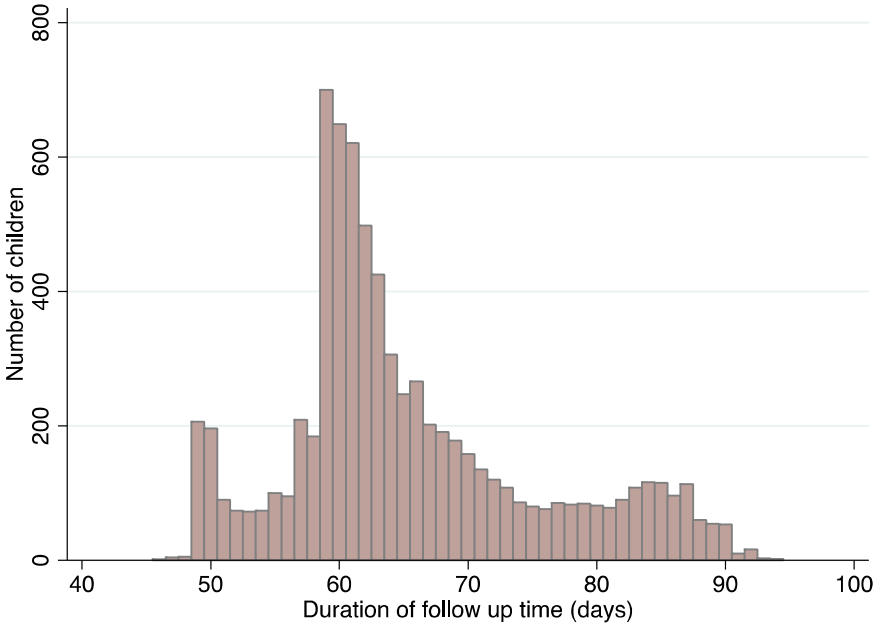


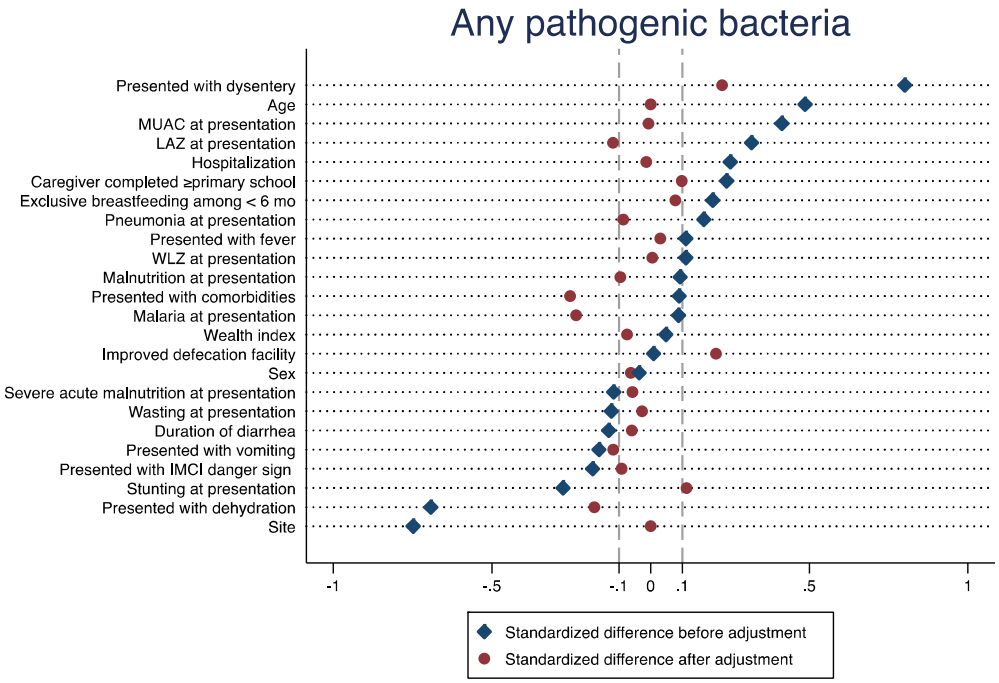
Table 2. Sensitivity analyses of the influence of an unmeasured confounder

Sensitivity analysis parameters			Results	
P_{unexp}	P_{exp}	RR_{C-O}	Rule-out RR	Bias (%)
0.10	0.15	1.5	11.0	2.4%
0.10	0.30	1.5	2.5	9.5%
0.10	0.50	1.5	1.7	19.1%
0.10	0.15	3.0	11.0	8.3%
0.10	0.30	3.0	2.5	33.3%
0.10	0.50	3.0	1.7	66.7%
0.10	0.15	5.0	11.0	14.3%
0.10	0.30	5	2.5	57.1%
0.10	0.50	5	1.7	114.3%
0.25	0.375	1.5	5.0	5.6%
0.25	0.75	1.5	1.6	22.2%
0.25	0.375	3	5.0	16.7%
0.25	0.75	3	1.6	66.7%
0.25	0.375	5	5.0	25.0%
0.25	0.75	5	1.6	100.0%
0.50	0.75	1.5	3.0	10.0%
0.50	0.75	1.5	3.0	25.0%
0.50	0.75	1.5	3.0	33.3%

Notation and interpretation:

- P_{unexp} = prevalence of unmeasured confounder in unexposed
- P_{exp} = prevalence of unmeasured confounder in exposed
- RR_{C-O} = association between outcome and unmeasured confounder
- RR_{E-O} = association between exposure and outcome
- Rule-out RR = the RR_{C-O} that would nullify the main effect (the strength of association between the unmeasured confounder with the outcome that would result in $RR_{E-O} = 1$)
- % Bias= percent of the observed association that is negated by the unmeasured confounder and calculated as: *(observed RR_{E-O} /true RR_{E-O}) -1)*

Figure 3. Covariate balance before and after propensity score adjustment within sub-groups by pathogen categories



A standardized difference between -0.1 and 0.1 is considered balanced

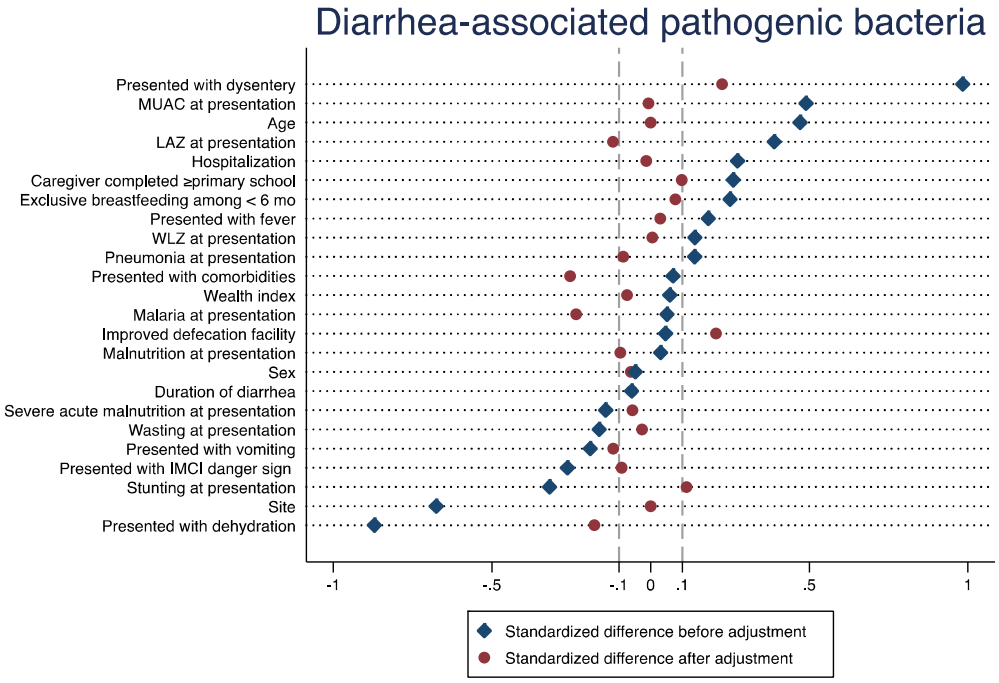


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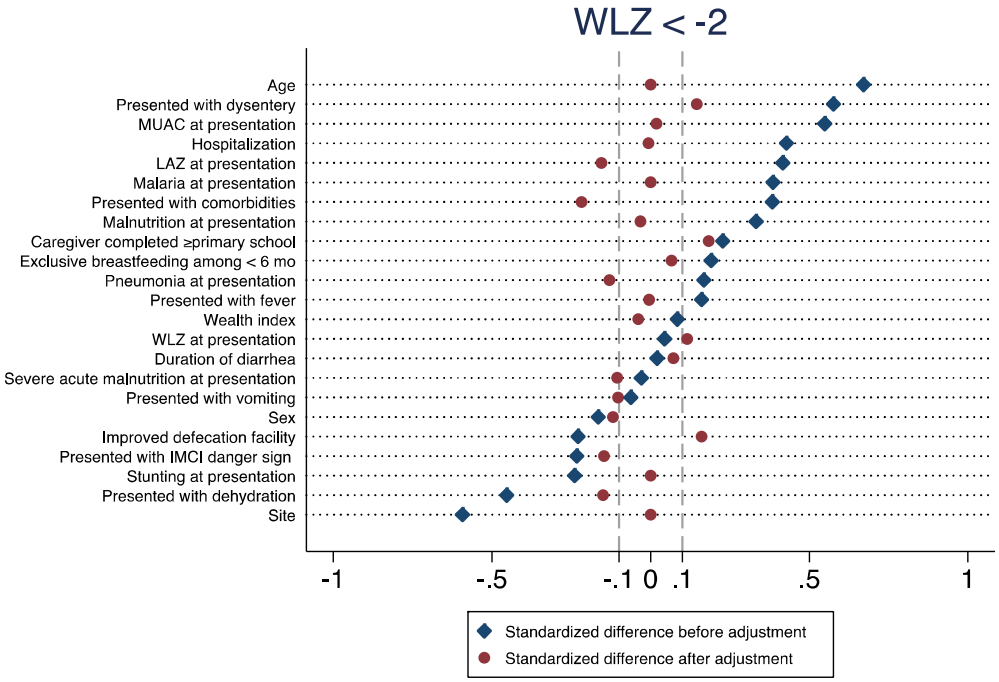
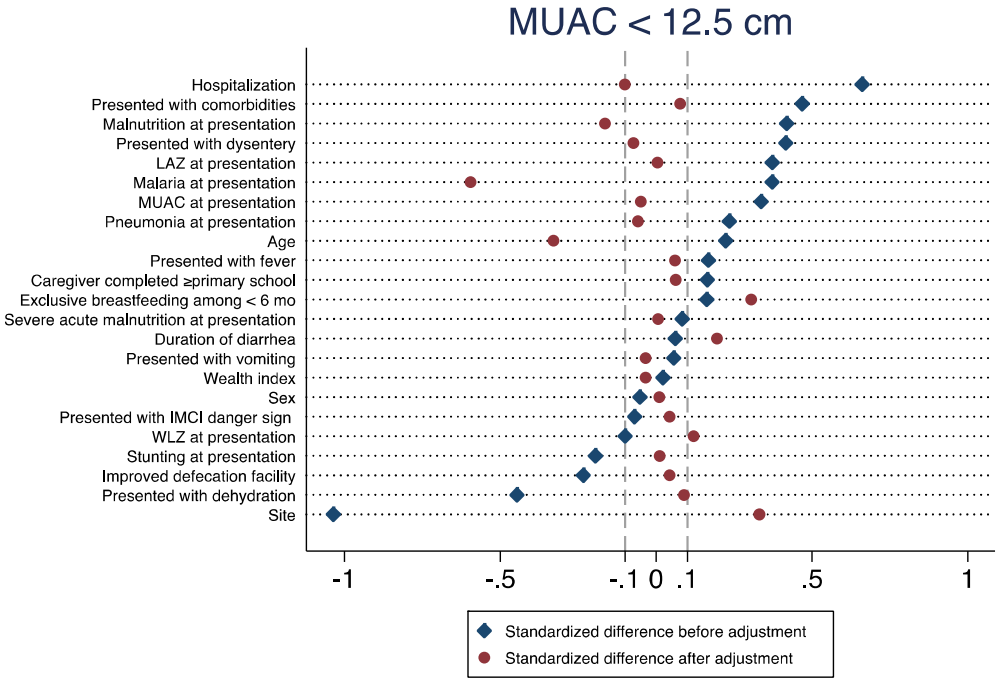
Figure 4. Covariate balance before and after propensity score adjustment within sub-groups by malnutrition category

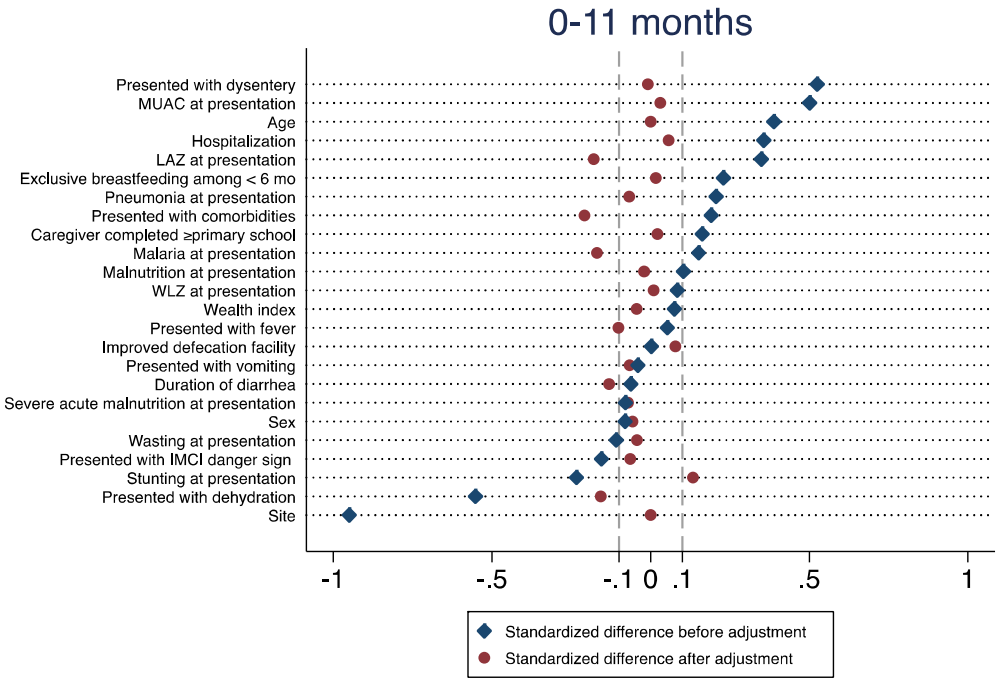


A standardized difference between -0.1 and 0.1 is considered balanced

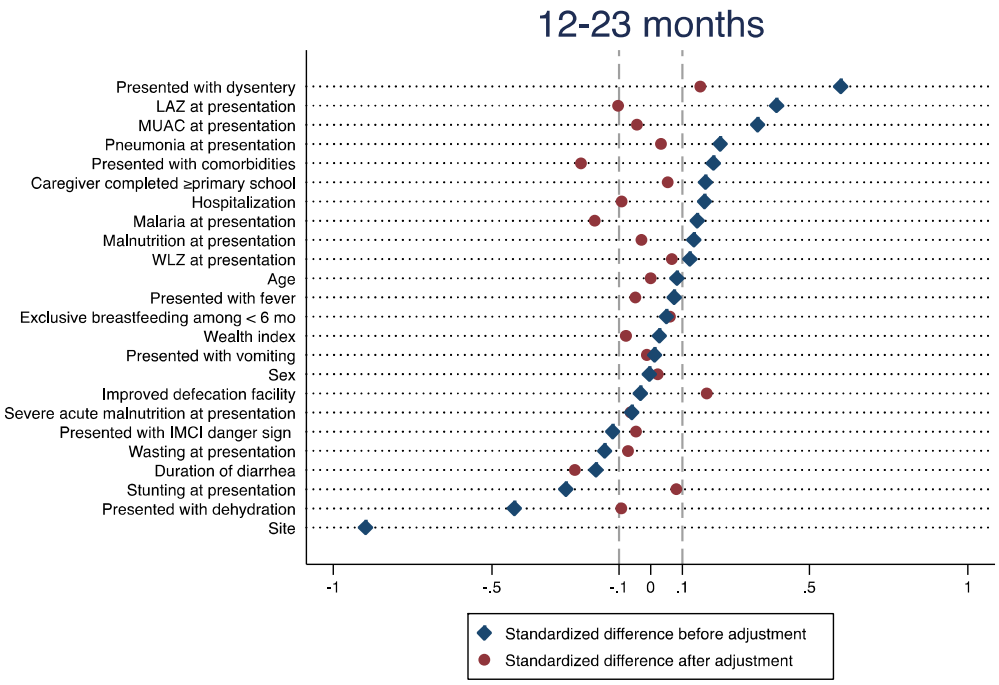


A standardized difference between -0.1 and 0.1 is considered balanced

Figure 5. Covariate balance before and after propensity score adjustment within sub-groups by age categories



A standardized difference between -0.1 and 0.1 is considered balanced



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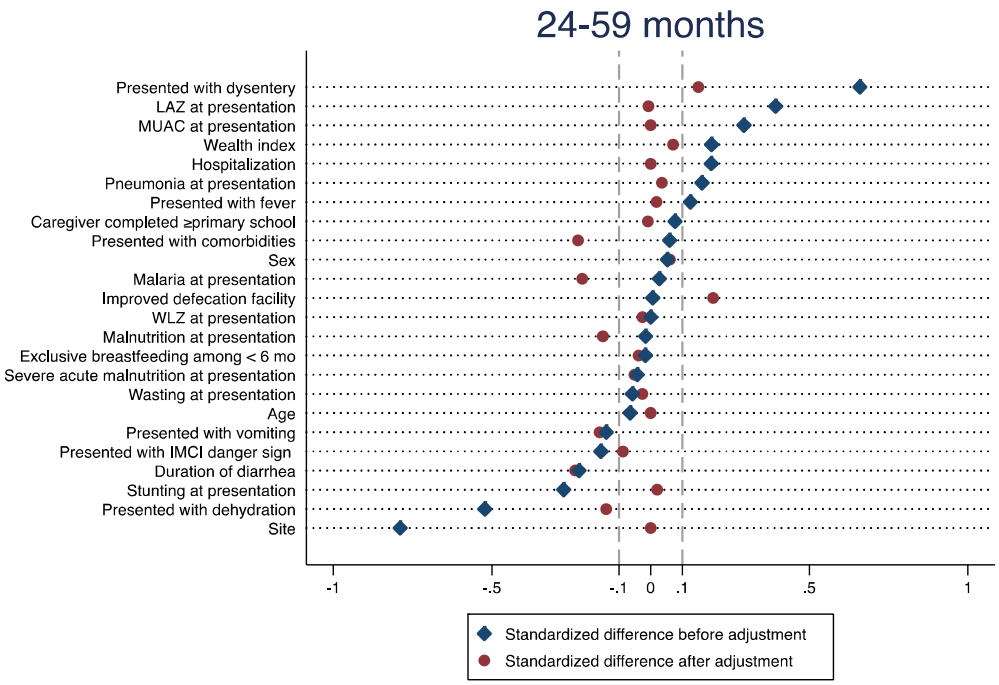
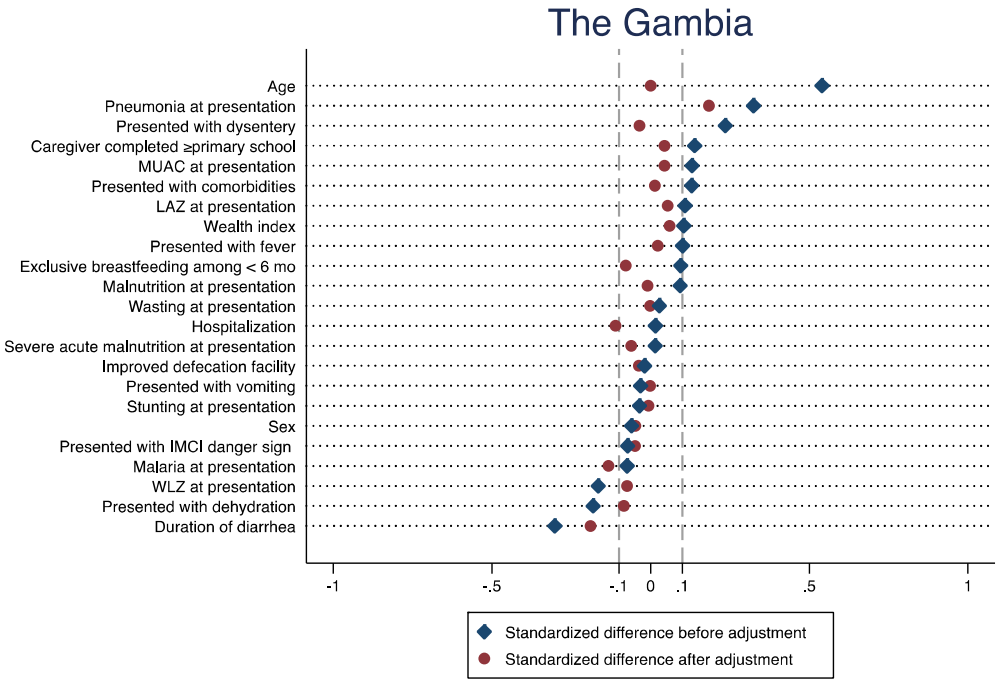
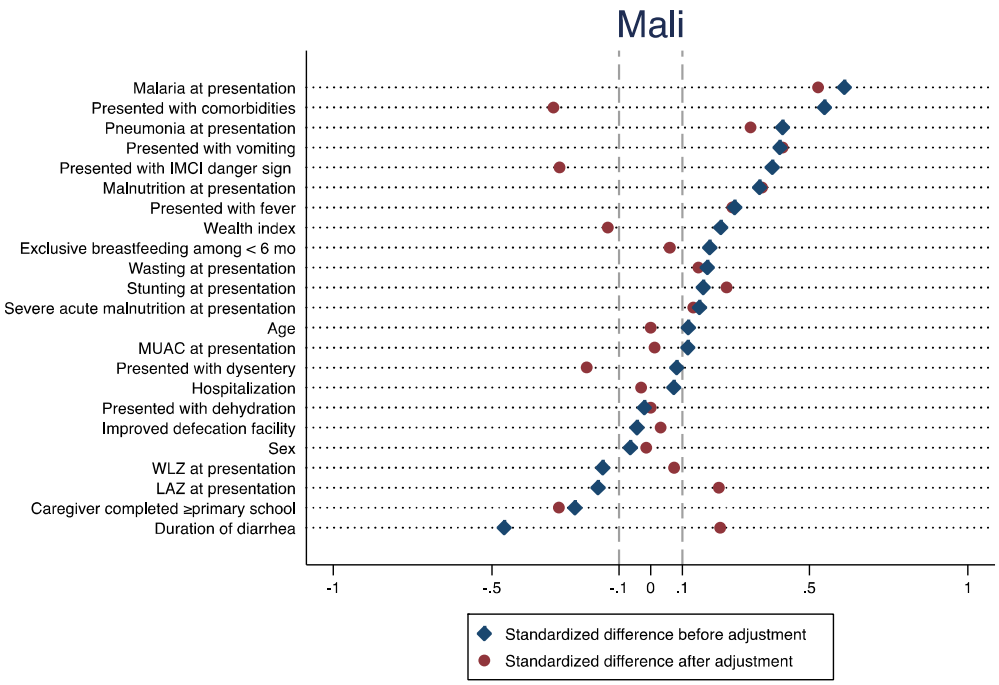


Figure 6. Covariate balance before and after propensity score adjustment within sub-groups by site categories





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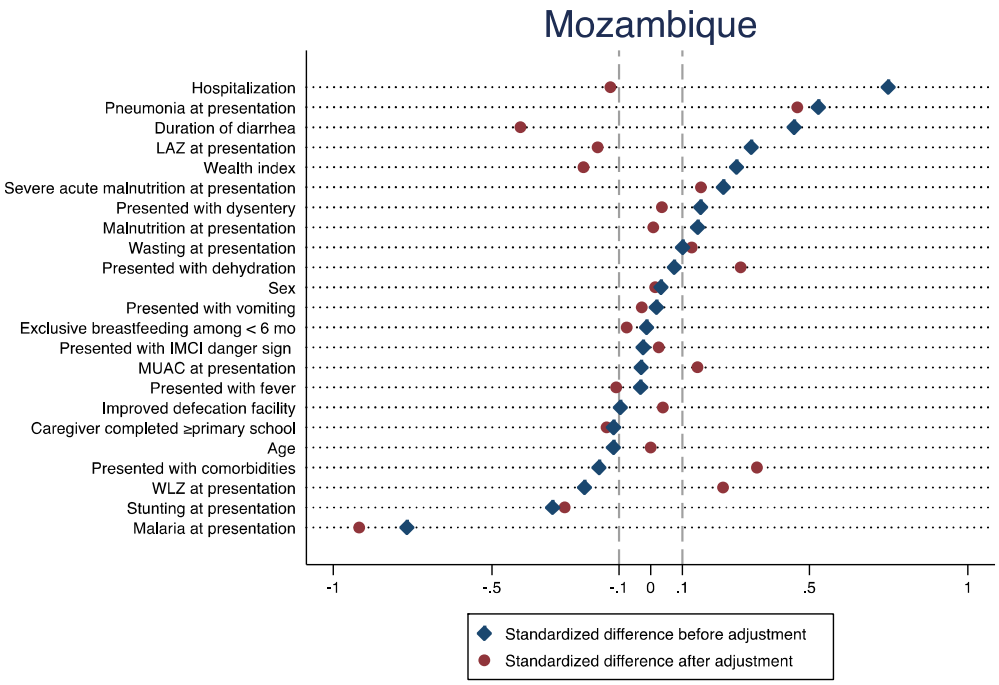

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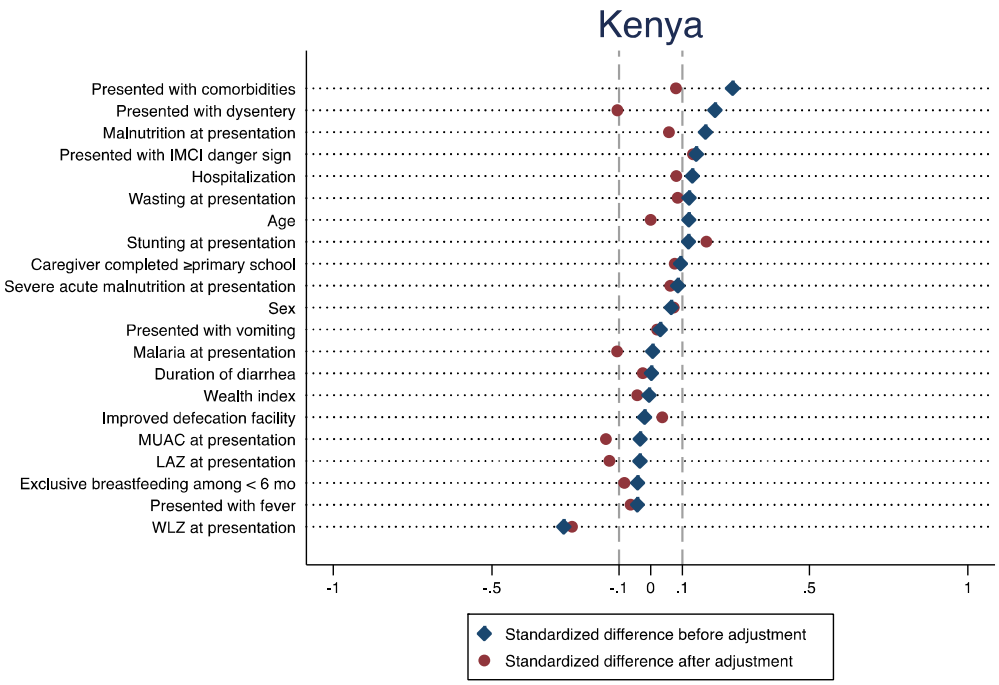

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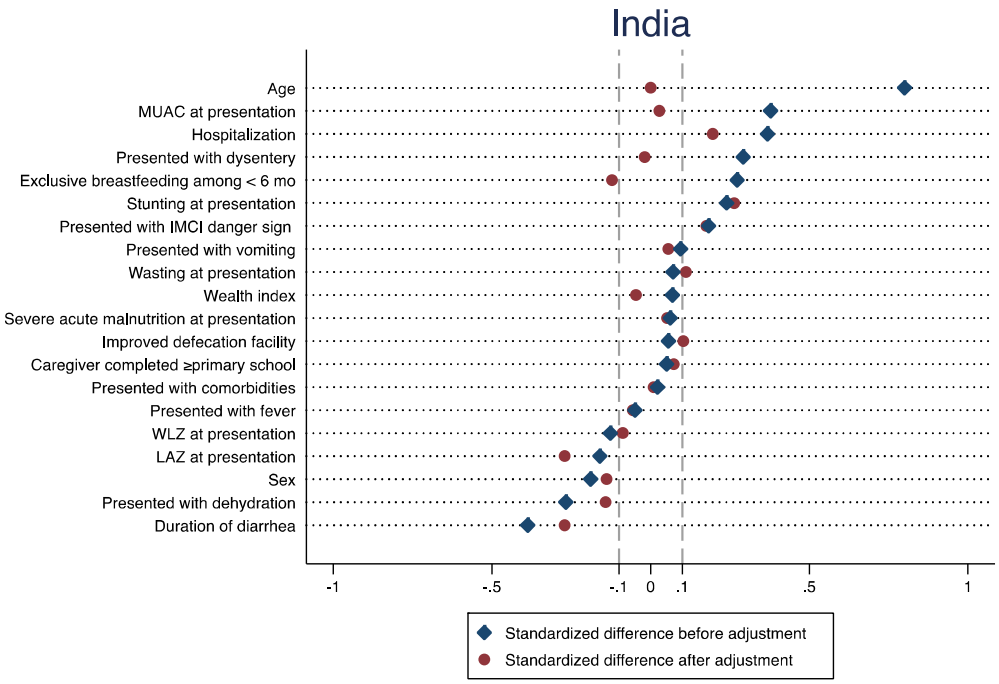

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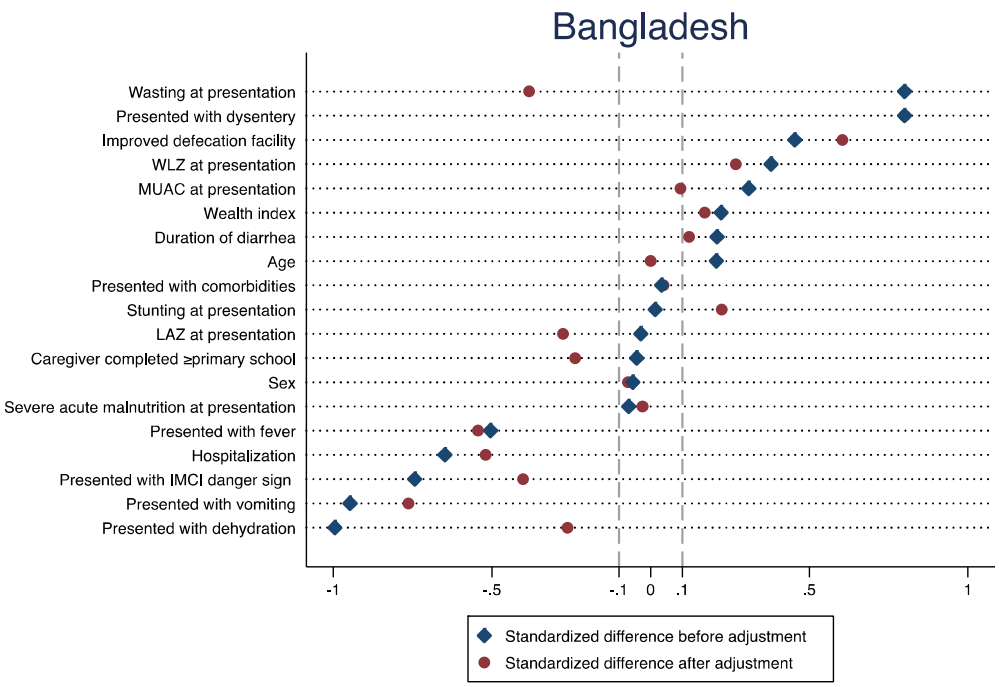

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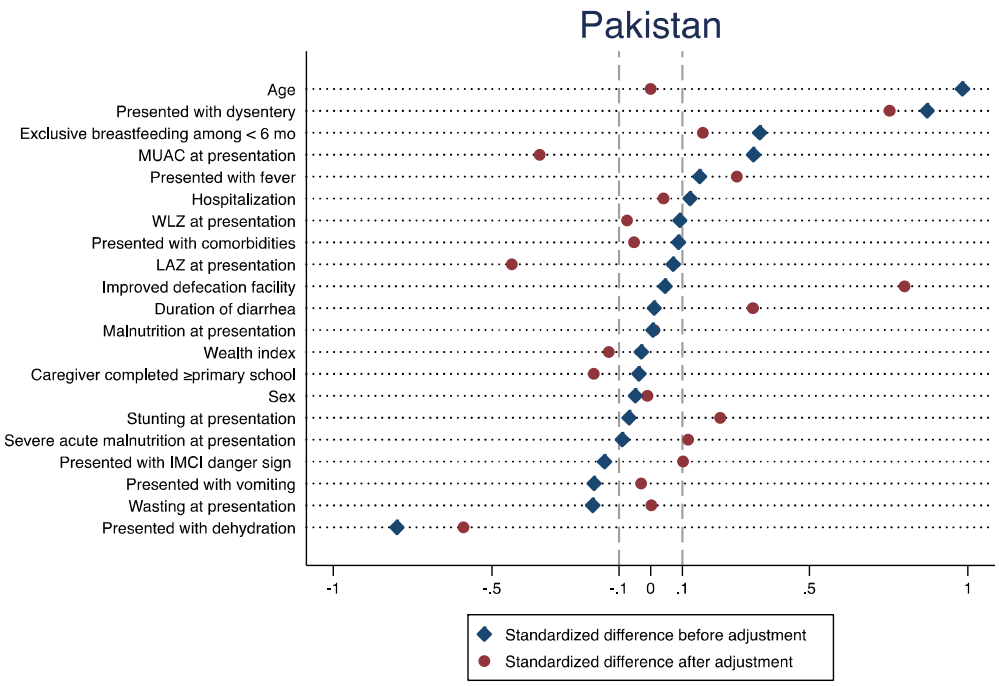


A standardized difference between -0.1 and 0.1 is considered balanced

CHAPTER 3

Evaluation of micro-cost data collection methods in low-resource settings: comparison of medical record abstraction and direct observation for ascertaining patient-level resource utilization data in a pediatric ward in western Kenya

ABSTRACT

Background

Micro-costing provides more accurate costing data than global estimates and the validity of cost data is critical to conducting accurate cost-effectiveness analyses. We compared two common methods for ascertaining patient-level cost data, direct observation of inpatient resource utilization and abstraction of resource utilization data from medical records.

Methods

Using micro-costing data collected among children 1-59 months old presenting with any infectious condition to a public hospital in western Kenya, we compared resource use ascertained from two methods for the same child: prospectively by direct observation of care or medical record abstraction. Resource use data was limited to the first day of the hospitalization. We calculated the proportion of resource data items that were observed that were also recorded on medical records. We used facility financial records to assign unit costs and calculate costs of care as ascertained by direct observation and by medical record abstraction. Differences in mean costs by the two methods were assessed using paired t-tests.

Results

Of 133 children included in the analysis, 55 (38.4%) had medical records that completely documented all resources utilized during the first day of hospitalization. Approximately 89.6% of medications observed were also documented in medical records, 88.5% of observed laboratory tests were documented, and 93.7% of observed procedures were documented. Mean costs of resources per child for the observed period were 983.68 ksh per direct observation and 866.54 ksh per medical record abstraction ($p < 0.0001$).

Conclusions

Micro-cost estimation by abstraction of resources documented in medical records may result in slightly underestimated costs, but the impact of these small differences in analyses may depend on the importance of the cost parameter in the analysis. Researchers should select the data collection method that best fits the needs of the study, balancing budget and staffing requirements against the importance of the cost parameters in the cost-effectiveness analysis.

INTRODUCTION

Cost-effectiveness analyses are important for resource allocations decisions in resource-limited health systems. One of the challenges to economic evaluation research in SSA is collecting quality cost data. Data on the net costs associated with an intervention are key inputs in cost-effectiveness models that are highly influential over the analysis' results; as such, poor data may lead to poor decisions. The net costs of the intervention include the cost of the intervention itself and the costs averted by the intervention's impact on resource use, which may be expected for preventative interventions that reduce morbidity and therefore prevent costly hospitalizations.

Micro-costing is a "bottom-up" approach that leads to precise estimation of patient-level cost data. This approach is particularly useful when costs are highly influential in a cost-effectiveness model or when an intervention is likely to impact resource use.[20,21] Patient-specific cost data also allow for more detailed analysis of variation in costs and cost-effectiveness, and capture components of cost more accurately and more comprehensively than top-down approaches.[98] However, micro-costing approaches are often inadequate in practice because they are resource-intensive.[99] Micro-costing in low-resource settings can be particularly challenging because of patient record and financial record availability and quality.[100–103] Accurate costing is particularly important in low-resource settings where ministries of health have limited resources to devote to health programs.

Little is known about which micro-costing methods are optimal for resource-limited settings. Two primary methods of ascertaining resource utilization data are direct observation of care and abstraction of care from medical records. Medical record abstraction may be faster and cheaper to conduct than direct observation, but depends on the completeness and accuracy of medical records. Understanding the strengths and limitations of these micro-costing methods in low-resource settings may inform future approaches to costing and allow for evaluating biases in previously collected cost data.

We sought to evaluate two methods for ascertaining patient-level resource utilization data for the purposes of micro-costing for an economic evaluation alongside a clinical trial - direct observation of care, and abstraction of medical records. We compared prospectively collected data on resource use ascertained by direct observation of care with retrospectively collected data on the same child for the same time period collected through medical record abstraction. We assessed completeness of medical records by estimating the proportion of directly observed care resources that were documented in medical records. We calculated two estimates of resource utilization costs for each child using data ascertained by direct observation of care, and using data ascertained per medical record abstraction. Finally, we also sought to estimate the costs of health worker personnel that contributed to overall hospitalization costs, in order to provide other researchers with estimates they may use in micro-costed estimates when direct observation of health worker time is not possible.

METHODS

Procedures and participant selection

The study was based in the pediatric ward of Kisii referral-level public hospital in the Nyanza region of western Kenya between April and December 2018. We included children in the observation if they were 1-59 months old and admitted to hospital for any condition except trauma or injury, poisoning, or birth defect . Children admitted during daytime hours (8 am to 6 pm) between April and December 2018 were included in the observation.

Patients were assigned a unique identifier number and were tracked using a color-coded sticker. No identifying information, clinical details, or hospital-assigned patient numbers were collected at

any time. This sub-study within the micro-costing was determined to be not human subject research, and written consent were determined to be unnecessary. Verbal consent was obtained from children's accompanying caregivers prior to observation.

Ascertainment of resource utilization

Direct observation began upon the patient's arrival at the pediatric ward. The data collector recorded the amount of time (rounded to the nearest minute) spent by clinical personnel on the care of the child and all resources utilized in the care of the child, including clerking and clinical history documentation, vital signs assessment, administration of medications, collection of samples for laboratory testing, medical procedures, and medical record documentation. Time spent by laboratory staff and pharmacy staff were not observed. Time spent by laboratory staff for various tests were ascertained by interviews with laboratory staff, but pharmacy staff were not available for interview, so time spent by hospital pharmacy staff on dispensing drugs was estimated through assumptions based on the opinion of other hospital staff. Children were directly observed on the first day of the hospitalization only. Observed began at admission and ended at the end of the work day (6 pm). The duration of observation therefore varied depending on the time the child was admitted. Medications were considered administered per direct observation if the observer observed the preparation and administration. Laboratory tests were considered administered if the observer observed the samples collected (blood), confirmed the order form with the staff, and observed the sample being transferred to laboratory staff. Procedure were considered observed if the observer observed it, or confirmed the work order with clinical staff and witness the child transferred to the relevant department.

Resources documented in medical records for this first day of care were then abstracted. Records were abstracted early in the morning on the second day of admission, or if records were not available at this time, were reviewed at discharge, only documenting resources used on the first day of the hospitalization. The medical records at this facility were organized by date, so it was feasible to identify the appropriate day.

We worked closely with hospital-based research staff and clinical staff to develop best practices for abstracting resource use data from medical records. The medical records at this particular facility were comprised of multiple documents, including a form documenting all prescribed medications the child is to receive during the hospitalization. This form, called the nurses' care sheet, is completed by the prescribing clinician at clerking, and is used by nurses to administer the medication throughout the hospitalization. We considered a medication to be administered per medical records if (1) there was evidence of administration on the nurse's care sheet (nurse initials, check mark or tick, or time administered) or (2) evidence of billing. Occasionally prescribed medications were not administered due to stock outs or, more commonly, the care plan was changed based on laboratory tests results or the opinion of a new managing clinician. Medications for which a prescription was recorded but were indicated to be out-of-stock, canceled, or not administered were considered not administered. Medications for which there was no evidence of administration were considered not administered. However, medications prescribed on an "as-needed" basis were often administered without documentation in practice, so we assumed these to be administered if they were prescribed on the nurses' care sheet regardless of evidence of administration. They were only considered to be missing from medical records if there was no prescription written on the nurses' care sheet.

There was no central document in the medical records that captured laboratory tests, so we identified information on laboratory tests if (1) the name of the test and the test results were written anywhere throughout the record, (2) the name of the test and the date of the test were written anywhere throughout the record, (3) a laboratory order form, receipt from the laboratory, or other

documentation from the laboratory was included or noted anywhere in the medical record, or (4) billing records were present that listed the name of the laboratory test.

Similarly, there were no central document in the medical records that captured procedures that occurred during the hospitalization. We identified information on procedures (1) if the medical records contained documents depicting details or results of the procedure (for example, a chest x-ray read-out or blood transfusion status notes), (2) the name and date of the procedure were written anywhere throughout the medical record, (3) an order form, receipt, or other documentation from the relevant department were included or noted anywhere in the record or (4) billing records were present that listed the name of the procedure.

Intake procedures were not observed due to the patient flow at this hospital. Intake procedures include triage and examination at the Maternal and Child Health office, where the decision to admit is made. All children who are admitted to hospital then undergo a cannulation before moving to the pediatric ward. Admission information is also documented at this point. Due to logistical challenges with identifying children at the MCH office, we considered "admission" to begin when the child and caregiver arrive at the pediatric ward. Thus, the costs of initial cannulation and the time involved for initial paperwork, triage, and examination were not included. Only re-cannulations (replacing a failed cannula with a new one once the child has arrived in the wards) were documented.

Estimation of costs

We then estimated costs of the first day of care by assigning a unit cost to each resource that was documented, separately for each data collection method. Unit costs were identified from financial records at the facility. Costs are presented in 2018 Kenyan shillings (ksh) and 2018 United States dollars (USD). For the analysis of components of total first-day hospital costs, we included costs of health worker time and daily bed charges, which are a flat rate charge of 800 ksh per child per day in the pediatric ward, to cover maintenance costs of the hospitalization such as laundry, janitorial services, electricity and water. To valuate health worker time, we used relevant estimates of health worker salaries from published literature,[105] because we were unable to access salary records for this facility.

Analysis

We calculated descriptive statistics of medical record completeness, defining completeness as:

$$\frac{Documented\ in\ both\ direct\ observation + medical\ records}{Documented\ in\ direct\ observation} \leq 1$$

We compared total costs for the first-day of the hospitalization as ascertained by medical record abstraction and direct observation. We used paired t-tests to estimate statistically significant differences between resource use costs as estimated by direct observation verses medical record abstraction. We also calculated the costs including the costs of personnel time, and disaggregated costs into components to identify the component that had greatest influence (drugs, laboratory tests, procedures, clinical staff time, laboratory staff time). We conducted a sensitivity analysis stratifying by the amount of time the child was observed, as not all children were observed for an entire day due to admissions late in the day. Analysis was done in Microsoft Excel and Stata SE 14.

RESULTS

One hundred thirty-six children were enrolled in this sub-study. Three children were excluded because no resources were observed during direct observation, resulting in 133 children in the analysis. The children were observed for an average of 4.8 hours on their first day of

hospitalization, with a median time observed of 4.3 hours and a range of 1.4 hours to 10.1 hours. During the time the child was observed on their first day of hospitalization, each child received an average of 3.8 medications, 1 procedure, and 2.8 laboratory tests (Table 1).

At the resource items level, 89.6% of observed medications were documented in medical records, 88.5% of observed laboratory tests were documented, and 93.7% of observed procedures were documented. At the child level, 87 (64.0%) children had all medical records that completely documented all drugs that were observed, 88 (64.7%) of children had medical records that completely documented all laboratory tests that were observed, and 132 (97.1%) had complete documentation of all procedures. Only 55 (38.4%) had medical records that completely documented 100% of all resources that were observed.

Mean total costs of resources per child for the observed period were 983.68 ksh per direct observation and 866.54 ksh per medical record abstraction. This corresponds to a relative difference in costs of 13.5% and an absolute difference in costs of 117.14 ksh ($1.14 USD). This difference was statistically significant per paired t-test ($p < 0.0001$) (Table 2). Although laboratory tests and drugs were equally likely to be missing from medical records, missing laboratory tests accounted for the greatest difference in costs (Table 2 and Figure 4), as these were much more expensive than drugs at this facility.

Median costs of health worker personnel during this first day of the hospitalization were 1387 ksh per child ($13.52 USD) (Table 3). This included a median of 933 ksh contributed by clinical staff time, 302 ksh contributed by laboratory staff time, and 134 ksh contributed by pharmacy staff time (Table 3). Total mean costs including resources ascertained by direct observation and the costs of all health worker personnel time were 2687.6 ksh/$26.18 (standard deviation: 1087.9 ksh/$10.60), with a range of 987.4 ksh/$9.62 – 4985.0 ksh/$48.56. When costs of health worker personnel were included, this accounted for the greatest proportion of total costs (Figure 5).

The amount of time each child was observed in our study did not appear to influence results for costs of resources (Table 4 and Figure 6).

DISCUSSION

Using data on inpatient resource utilization among children admitted for any infectious condition to a public hospital in western Kenya, we compared costs ascertained by two micro-costing methods and assessed the completeness of medical record documentation of resource utilization. We reported a small degree of missingness of resource utilization data in medical records, and thus mean total costs per child were slightly lower when using data abstracted from medical records than when using data ascertained by direct observation. We also found the costs of health worker personnel time accounted for the greatest proportion of first-day resource costs in this analysis.

We reported that nearly two-third of children's records were missing documentation of at least one item, and approximately 10% of items were missing from medical records. These results are consistent with other research evaluating completeness of medical records in LMICs. An analysis of 155 inpatient records at a Tanzanian hospital reported approximately 50% of patient records had 3 or more sections that were incompletely documented.[106] A data quality assessment of 1,482 paper and electronic medical records in 27 facilities in Kenya reported at least 31% of records had at least one missing data item.[107] An analysis of electronic medical records in 90 facilities in Haiti reported approximately 10-50% missingness of clinical data.[108] A study based at five maternal and child outpatient centers in western Kenya reported 60% of antenatal records were

missing data.[109] Another study in four facilities in Zimbabwe reported a range of approximately 5-60% missingness of information in medical records of voluntary medical male circumcision.[110] Due to the missingness we report, we found mean costs were 13.5% lower when abstracted by medical records rather than directly observed. However, the absolute difference was small (~$1). While direct observation may result in more accurate cost data, the impact of this slight discrepancy may depend on how influential the cost parameter is in a given analysis. Analysts may assess the influence of cost parameters in their models as well as account for parameter uncertainty through sensitivity analyses.[21,111] Our results suggest that, in order to account for the possibility that medical records may underestimate costs, economic evaluations using patient-level data from medical record abstraction costing could consider conducting sensitivity analyses varying cost parameters by at least 15%. Analyses that include adequately wide sensitivity ranges of cost data may account for both the possibility of measurement error based on medical record incompleteness as well as heterogeneous costs. While the focus of this analysis has been evaluation of data relevant to micro-costing and thus we did not assess completeness of other clinical data, the missingness we report may also impact results when medical records are used for other purposes, such as ascertaining data on epidemiologic exposures or important confounding factors. Analysts could consider the impact of data quality issues and potential measurement error in their analyses possibly resulting from medical record incompleteness.

We have identified several drivers of resource costs – costs of laboratory tests and health worker personnel time. Laboratory tests were the most expensive items at this facility, and any missingness of laboratory tests resulted in relatively great differences in costs. Micro-costing studies should identify the components that contribute most to overall costs, assess for potential measurement error in costing processes, and work closely with hospital-based staff to develop methods to ensure items in this component are ascertained as accurately and completely as possible. We also report health worker personnel time accounted for the greatest proportion of costs when included. Other micro-costing studies have reported health worker personnel time to be the largest driver of costs in LMICs.[101–103,112,113] Micro-costing studies should ensure the costs of personnel time are included, whether ascertaining health worker time through direct observation, through interviews with health workers, or with assumptions based on available literature.

Micro-costing studies are more often employed in economic evaluations set in LMICs than those in middle- or high-income countries,[27] but sparse data are available that compare results of various methods for ascertaining micro-costing data in resource-limited settings. This highlights the need to identify micro-costing methods that are both accurate and practical in low-resource settings. Micro-costing through direct observation is likely to result in the most accurate, precise cost estimates but requires a substantial amount of research staff time. Micro-costing by medical record abstraction is therefore likely to be much less costly to research budgets. We estimate it takes a data collector approximately 15 minutes to fully abstract resource use data from the medical records at this facility, but the time requirement to directly observe a 3-day hospitalization, for example, would be approximately 72 hours. While we did report some incompleteness of medical records, micro-costing through medical record abstraction may still result in more precise data than gross-costing approaches. Micro-costing by medical record abstraction may be a more feasible option to collect precise patient-level data when research staff and budgets are not able to support direct observation costing. Researchers should weigh the importance of precise, accurate cost data in their research project against the budget and staffing requirements for data collection by direct observation.

There are important limitations to this work to consider. First, we are only able to ascertain the proportion of resources that were observed that were documented in medical records and cannot

assess the proportion of resources that were documented in medical records that were actually administered. We only observed children on the first day of the hospitalization, and, while this time period is expected to be the most resource-intensive, we cannot predict what results would be for the hospitalization overall. The costs presented in the analysis are not comprehensive total costs, as we excluded overhead and capital costs, out-of-pocket costs to the patient, and costs of triage. These results and conclusions may be facility-specific and thus may not be generalizable. We have data from only one facility, a public hospital in a rural region of Kenya, and our approach to abstracting data from medical records was highly specific to the medical record keeping at this facility. Results may be different in settings with different billing systems or different record-keeping practices.

CONCLUSION

Micro-costing through medical record abstraction may result in slightly underestimated costs than micro-costing through direct observation, due to incompleteness in documentation of resource utilization. However, the impact of this incompleteness on analyses may depend on the goals of the analysis, and the choice of micro-costing method should weigh the research budget limitations against the importance of the cost parameters in a model. More comprehensive studies that include multiple sites and observe children through the entire hospitalization will be needed to confirm the internal and external validity of these results.

TABLES AND FIGURES

Table 1. Resource utilization ascertained per direct observation among children 1-59 months old admitted to hospital in western Kenya for any infectious condition.

	Frequency		
	Median (IQR)	Min-max range	Mean (SD)
Number of drugs observed	4 (3,5)	0,9	3.8 (1.56)
Drug type	n	(% of 133 children)	
Benzylpenicillin	92	69.2%	
Gentamycin	97	72.9%	
Paracetamol	92	69.2%	
Ceftriaxone	33	24.8%	
Artesunate	20	14.3%	
Ringer's lactate	20	14.3%	
Phenobarbital	14	10.5%	
ORS	14	10.5%	
Zinc	14	10.5%	
Oxygen	10	7.5%	
Normal saline	10	7.5%	
Salbutamol	9	6.8%	
Prednisone	8	6.0%	
Nystatin	7	5.3%	
Fluconazole	6	4.5%	
Metronidazole	6	4.5%	
F75 or F100 nutrition	4	3.0%	
Other*	24		
Number of lab tests	3 (2,4)	0, 5	2.76 (1.07)
Test type			
Full hemogram	126	94.7%	
Blood smear test for malaria parasites	106	79.7%	
Blood grouping/cross match	13	9.7%	
Provider-initiated testing and counseling (PITC)	10	7.5%	
Urinalysis	5	3.8%	
Gene Xpert test	4	3.0%	
Cerebrospinal fluid analysis	1	0.8%	
Stool test for ova & cysts	1	0.8%	
Number of procedures	1 (1,1)	0, 2	0.97 (0.33)
Procedure type	n	%	
Vital signs assessment	123	92.5%	
Chest x-ray	17	12.8%	
Lumbar puncture	11	8.3%	
Blood transfusion	4	3.0%	
Re-cannulation	3	2.3%	
Gastric tube placement	1	0.8%	

*Includes dexamethasone (n=3 [2.3%]), lactoluse (n=2 [1.5%]), ranferon (n=2 [1.5%]), multivitamin (n=2 [1.5%]), morphine (n=1 [0.8%]), floxinide (n=1 [0.8%]), ranitidine (n=1 [0.8%]), atropine (n=1 [0.8%]), azithromycin (n=1 [0.8%]), probeta (n=1 [0.8%]), esomeprazole (n=1 [0.8%]), folic acid (n=1 [0.8%]), piriton (n=1 [0.8%]

Figure 1. Completeness of documentation of items in medical records of children 1-59 months old admitted for any infectious condition in western Kenya

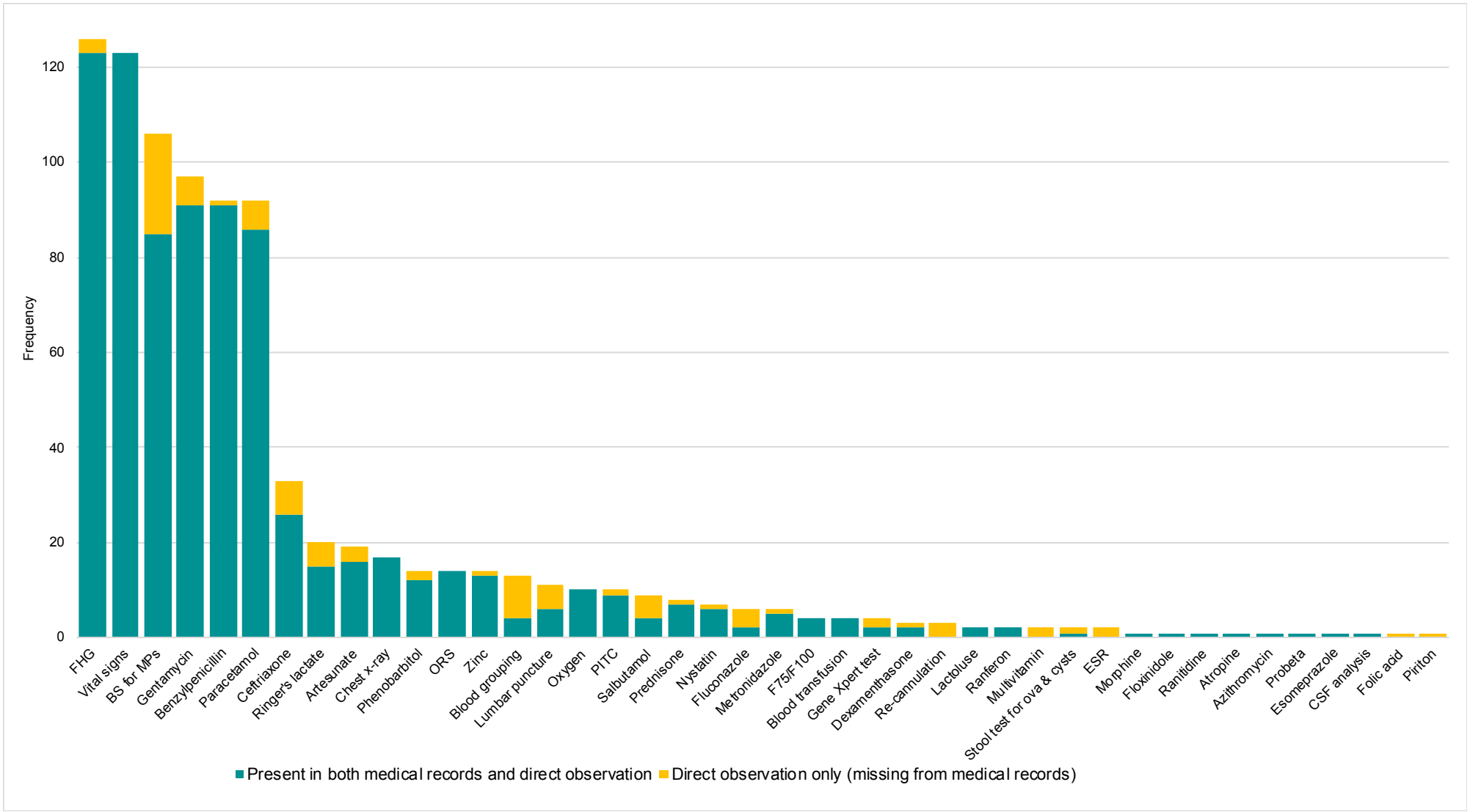


Figure 2. Completeness of documentation of resource utilization in medical records, at the child level (A) and at the resource level (B)

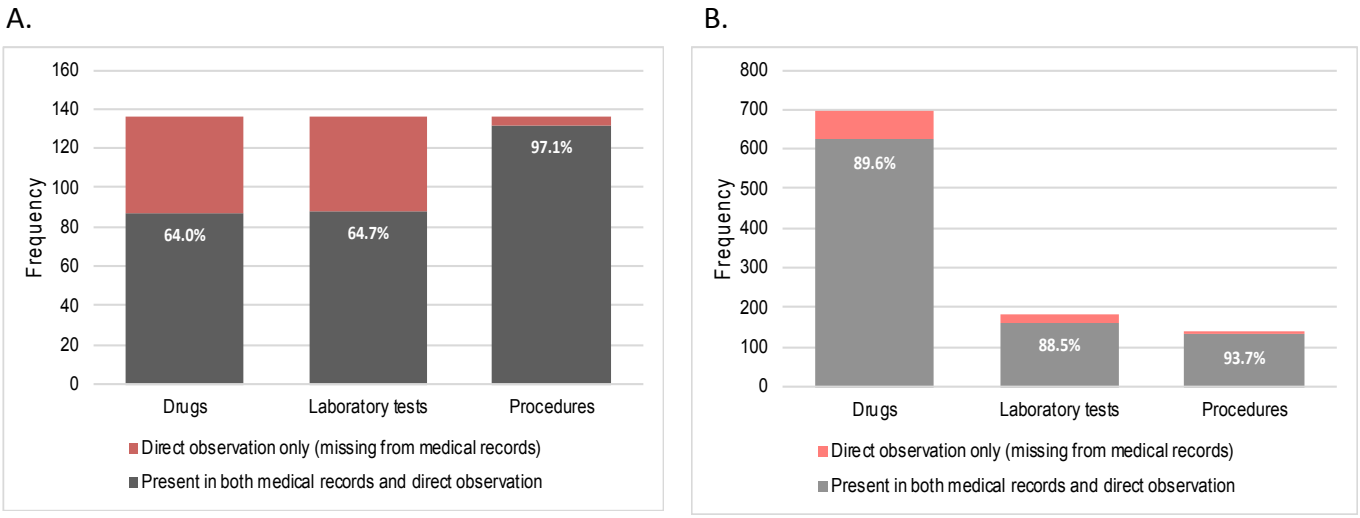


Figure 3. Distribution of resource utilization costs during the first day of hospitalization per child as ascertained by data ascertainment method

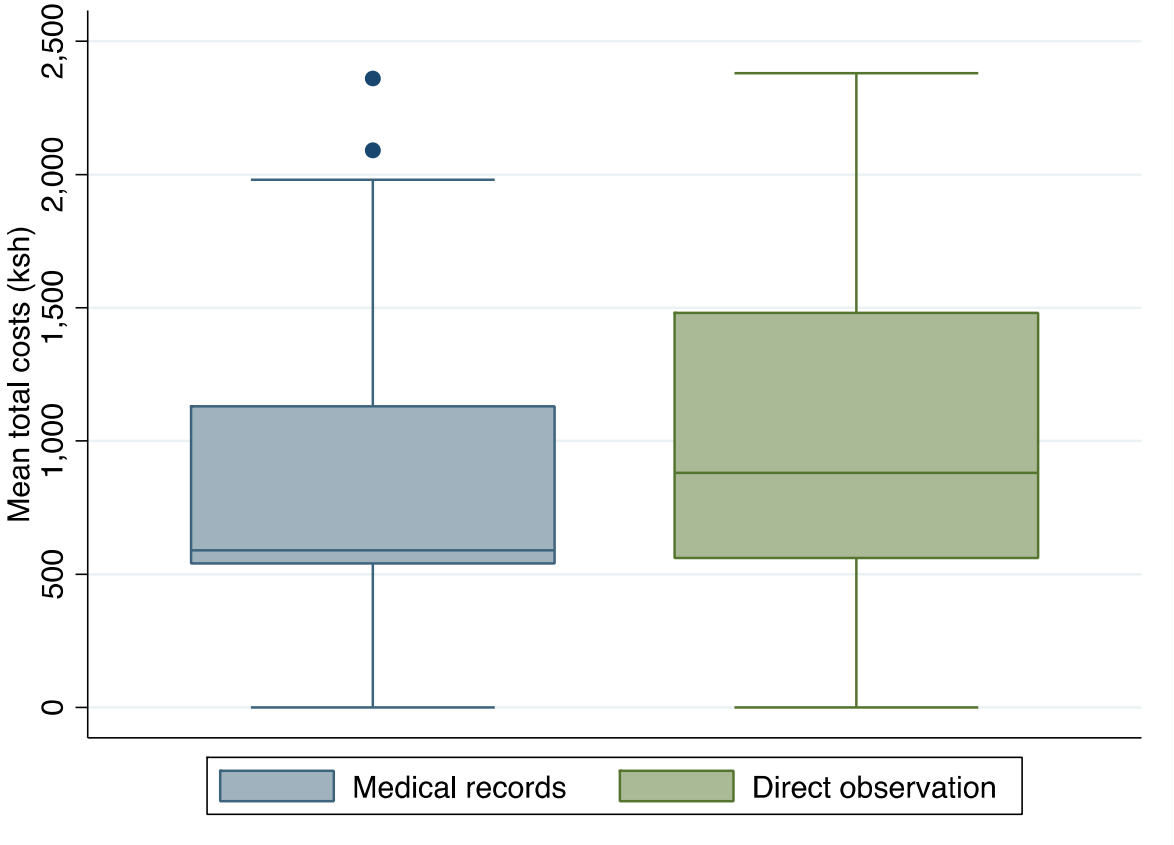
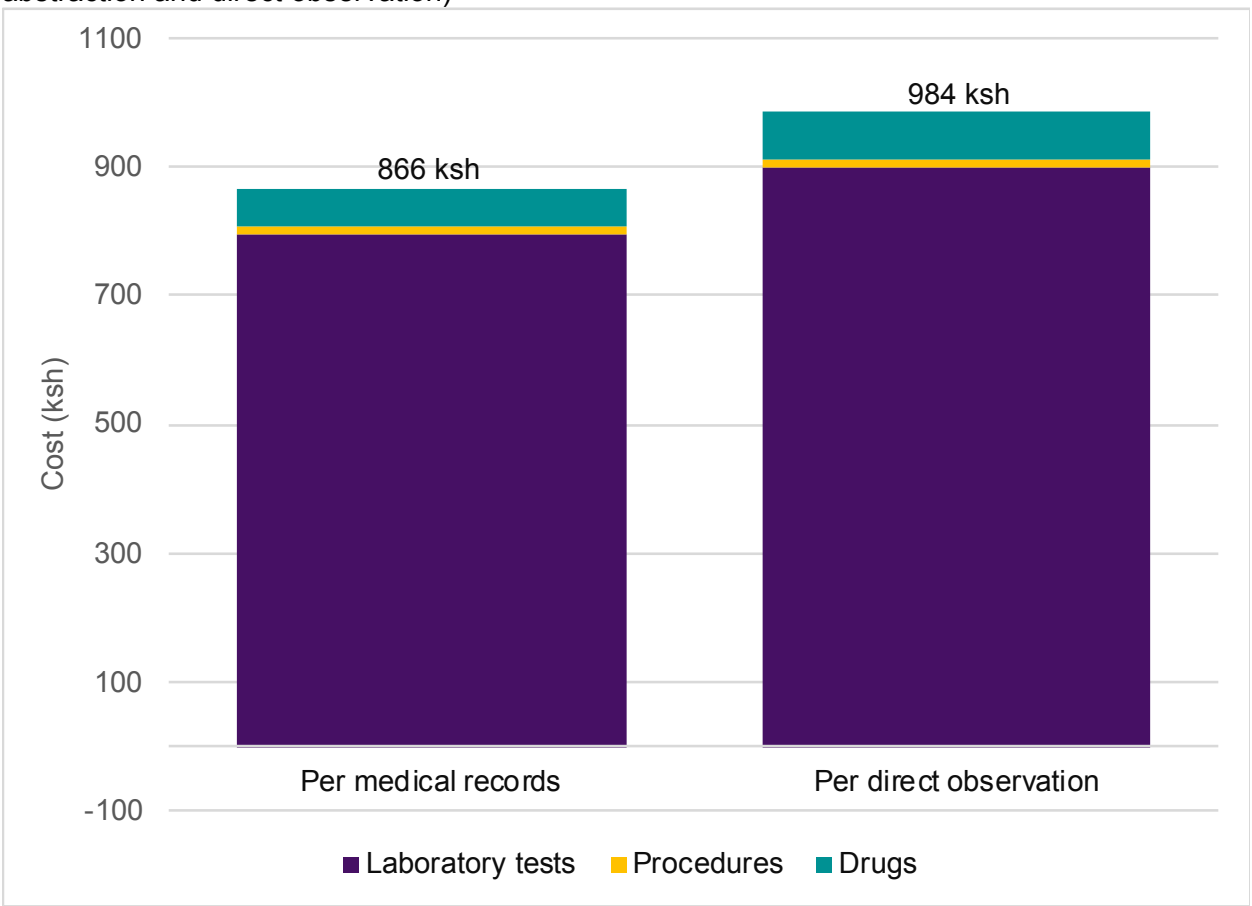


Table 2. Comparison of mean costs of resources utilized during the first day of hospitalization among children in western Kenya

	Costs of resources abstracted from medical records (ksh/USD)	Costs of resources directly observed (ksh/USD)	Difference (ksh/USD)	p-value from paired t-test
Laboratory tests	796.32 ksh/$7.80	899.26 ksh/$8.81	102.9 ksh/$1.01	p < 0.0001
Procedures	9.78 ksh/$0.09	13.24 ksh/$0.13	3.45 ksh/ $0.03	p=0.03
Drugs	60.44 ksh/$0.59	71.18 ksh/$0.70	10.74 ksh/$0.11	p < 0.0001
Total	866.54 ksh/$8.49	983.67 ksh/$9.64	117.13 ksh/$1.15	p < 0.0001

Figure 4. Mean costs of first day of pediatric hospitalizations by data ascertainment method (medical record abstraction and direct observation)



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Drugs	60.44 ksh/$0.59	72.18 ksh/$0.70	10.74 ksh/$0.11	p < 0.0001
Total	866.54 ksh/$8.49	983.67 ksh/$9.64	117.13 ksh/$1.15	p < 0.0001

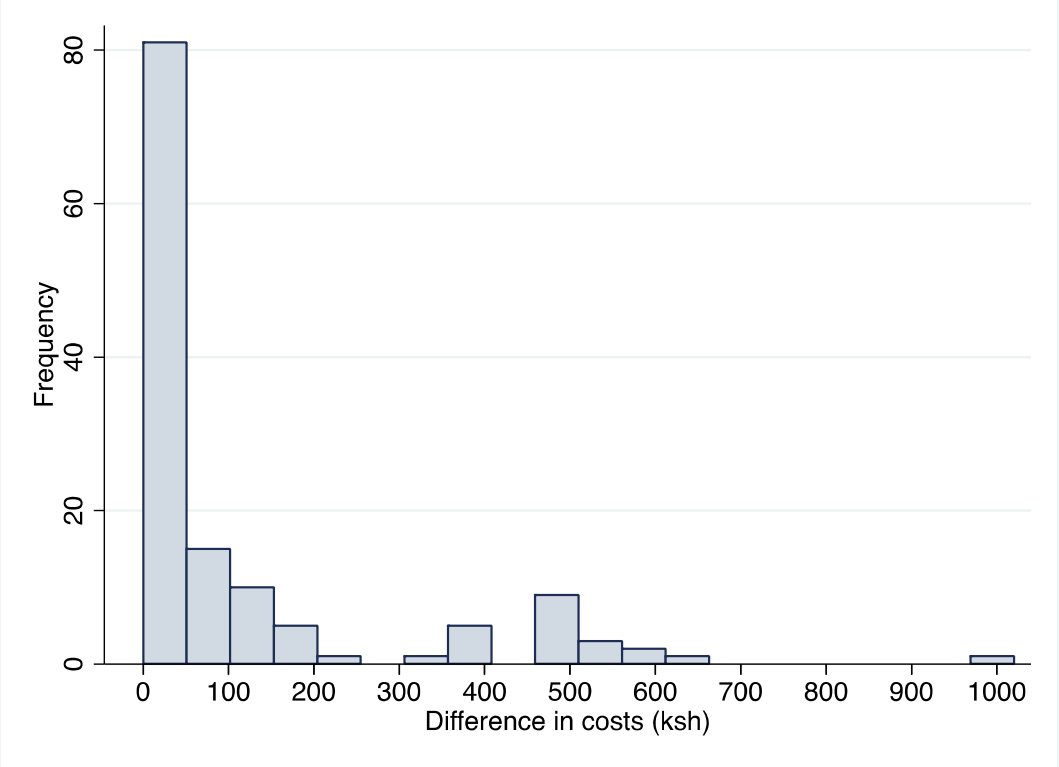


Table 3. Costs of health worker personnel time during the first day of pediatric hospitalizations in western Kenya

Note: Clinical staff includes nurses, clinical or medical officers, and physicians

	Median time (IQR), minutes	Median costs of time (IQR), ksh	Median costs of time (IQR), USD
Clinical staff	88.8 (75.1, 103.88)	932.9 ksh (805.4 ksh, 1247.6 ksh)	$9.20 ($7.85, $12.16)
Laboratory technicians	67.5 (30, 82.5)	301.6 ksh (301.6 ksh, 368.3 ksh)	$2.94 ($2.94, $3.59)
Pharmacy technicians	30 (30, 30)	134.4 ksh (134.4 ksh, 134.4 ksh)	$1.31 ($1.31, $1.31)
Total	165.6 (140.2, 195.8)	1387.15 ksh (1178.9 ksh, 1650.8 ksh)	$13.52 ($11.49, $16.09)

Figure 5. Cost components that comprise resource utilization costs during the first day of hospitalization among children in western Kenya, including the costs of resources and health worker personnel time

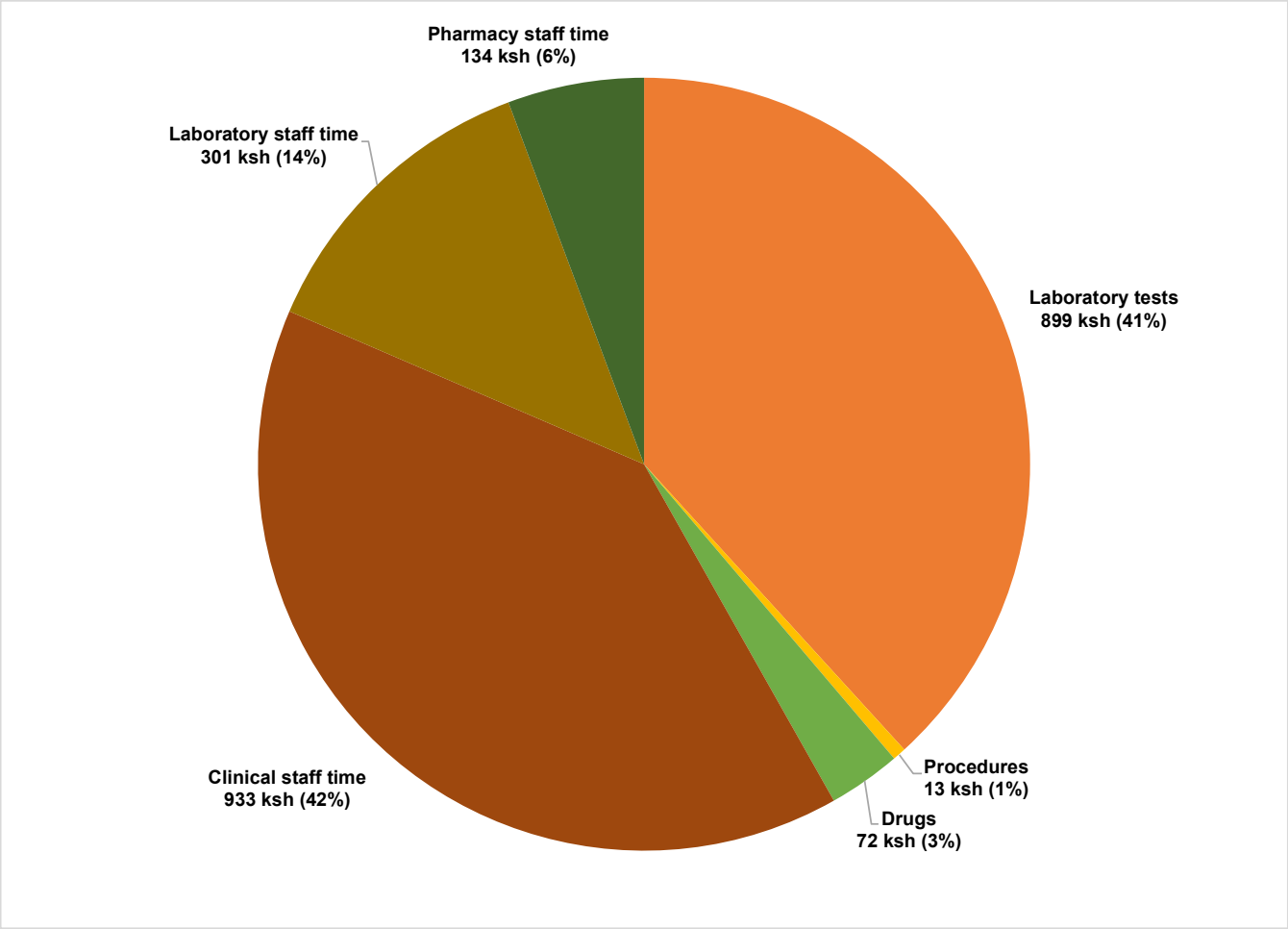
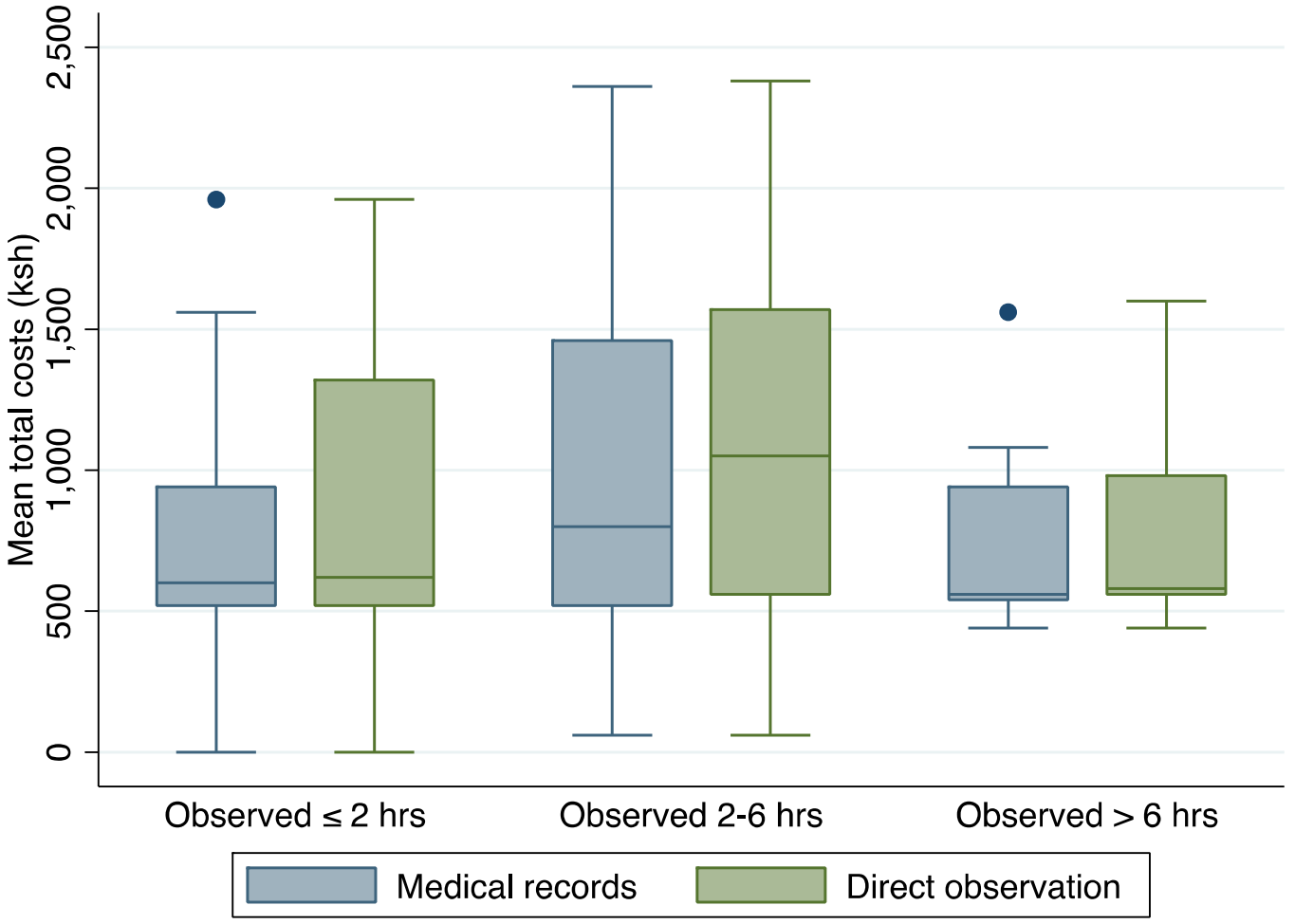


Table 4. Comparison of mean costs of resources utilized stratified by amount of time observed

	Costs of resources abstracted from medical records (ksh/USD)	Costs of resources directly observed (ksh/USD)	Difference (ksh/USD)	p-value from paired t-test
Among children observed ≤ 2 hours (n=10)	738.75/$7.24	800.0/$7.84	61.25 ksh/$0.60	p=0.0075
Among children observed 2-6 hours (n= 78)	992.73/$9.73	1143.92/$11.21	151.19 ksh/$1.48	p < 0.0001
Among children observed > 6 hours (n=44)	790.23/$7.74	893.46/$8.76	103.23 ksh/$1.01	p < 0.0001

Figure 6. Distribution of resource utilization costs per child as ascertained by medical records vs direct observation, stratified by time observed



APPENDIX

Appendix table 1. Directly observed estimates of time spent by clinical staff for various care activities

	Cadre	N	Median (interquartile range)	Min, max	Mean (SD)
Time per drug administration	Nurse	693 drugs among 133 children	5 (3,8)	2, 40	7.14 (7.65)
IV drug		307 drugs among 44 children	4 (2.5, 7)	1, 17	6.3 (7.1)
Among those with 1 IV drug		4 drugs among 4 children	3.5 (3, 5)	2, 6	3.9 (1.4)
Oral drug		162 drugs among 33 children	5 (4,6)	2, 30	6.76 (6.53)
Intramuscular injection		10 drugs among 3 children	3 (2,7)	2, 7	4 (2.65)
Time per sample collection for lab tests	Nurse	117 children			
Blood collection		117 children	5 (3,6)	2, 30	6.0 (5.15)
Blood collection for 1 test only		9 children	4 (4, 5)	2,8	4.7 (2.1)
Cerebrospinal fluid		1 child	5		
Urine		1 child	3		
Stool		1 child	8		
Time for clerking	Clinical officer	125 children	45 (38, 58)	25, 112	51.05 (20.1)
Time for nursing documentation	Nurse	83 children	21 (9, 28)	4, 32	19 (10.6)
Time for procedure	Varies	123 children	37 (27, 47)	5-101	39.5 (20.1)
Vital signs	Nurse		3(2,3)	2, 6	3.14 (1.35)
Lumbar puncture	Clinical officer	14 children	16.5 (13, 20)	13, 20	16.5 (4.95)
Blood transfusion	Clinical officer, nurses	4 children	25 (18, 45.5)	14, 63	31.75 (21.6)
Chest x-ray	Not conducted in wards	0	Not available		
Re-cannulation	Clinical officer or physician	4 children	10 (7, 20)	4, 50	15.7 (14.5)
Gastric tube placement	Clinical officer or physician	3 children	11 (8, 26)	8, 26	15 (9.6)

Appendix table 2. Health worker-reported estimates of time spent by laboratory staff and pharmacy staff

Laboratory staff		
Laboratory test	Active time (min)	Source of time estimates
Full hemogram	30	Per laboratory technician report
Blood smear for malaria parasites	30-45	Per laboratory technician report
Blood grouping/cross-match	60	Per laboratory technician report
Provider initiated testing & counseling (PITC)	30-45	Per laboratory technician report
Urinalysis	30	Assumption
Gene Xpert test	120	Assumption
Cerebrospinal fluid analysis	60	Per laboratory technician report
Erythrocyte sedimentation rate	60	Per laboratory technician report
Random blood sugar	10	Per laboratory technician report
Hemoglobin	15	Per laboratory technician report
Stool test for ova & cysts	20-30	Per laboratory technician report
Sickle cell test	90	Per laboratory technician report
Child HIV test	30-40	Per laboratory technician report
Pharmacy staff		
Dispensing several drugs (≤2)	15	Assumption
Dispensing many drugs (>2)	30	Assumption

Appendix table 3. Monthly salaries for healthcare workers in Zambia (includes allowances and base salary)

	As presented in McCoy et al (2005 USD)	**Adjusted to 2018 USD**	**Hourly (based on 45 hr work week)**
Clinical officer	350	470	2.61
Nurse	350	470	2.61
Laboratory technologist	350	470	2.61
Pharmacy technician	350	470	2.61
Physician	1450	1947	10.82

Appendix table 4. Unit costs for care items per financial records at the facility

Item		Cost
Drugs*		20
Other treatments		
	F75/F100	2 per ml
	Oxygen	200
	Intravenous fluids - Normal saline and ringer's lactate	50
Laboratory tests		
	Random blood sugar test	100
	Blood smear for malaria parasites	100
	Cerebrospinal fluid analysis	400
	Erythrocyte sedimentation rate test	600
	Full hemogram	400
	Blood grouping/cross-match	500
	Liver function test	400
	Provider initiated testing and counseling (PITC)	0
	Stool test for ova and cysts	100
	Sickling test	200
	Urinalysis	100
Procedures		
	Cannula	40
	Gastric tube placement	310
	Blood transfusion	250
	Chest x-ray	400
	Lumbar puncture	400

*All drugs are charged at a flat rate of 20 ksh each at this facility

CHAPTER 4

Projected impact and comparative cost-effectiveness of community-based versus targeted administration strategies for reducing child mortality in sub-Saharan Africa

ABSTRACT

Background

Azithromycin (AZM), delivered through mass drug administration (MDA) platforms, has been shown to reduce child mortality in sub-Saharan Africa (SSA). However, such a strategy would expose many children to AZM, many of whom would not be likely to benefit. Concerns about potential adverse events and emergence of macrolide resistance have also led to studies of more targeted AZM administered to high-risk children. To illustrate the health impact and resource implications of targeted vs population-based strategies, we modeled the cost effectiveness of MDA to children 1-59 months of age, MDA to children 1-5 months of age, AZM administered at hospital discharge, and the combination of MDA and post-discharge AZM.

Methods

Cost-effectiveness was modeled from a payer perspective with a 1-year time horizon, and was presented as cost per DALY averted and per death averted. The model included the impact of macrolide resistance, adverse events, hospitalization, and mortality, and the cost of AZM delivery and healthcare utilization. Model parameters were sourced from published data. We conducted deterministic and probabilistic sensitivity analyses.

Results

Using estimates of base-case 1.64% mortality risk in the population of children 1-59 months old, 3.1% in the population of children 1-5 months old, 4.4% mortality risk post-discharge among the 7% of the population that is hospitalized in a 1-year period, and a mortality reduction of 13.5% derived from recent clinical trial results, we found the deaths averted by post-discharge AZM would be equivalent to 0.02% of the under-5 population, at a cost of $9.00/DALY (95% uncertainty interval [UI]: 4.78, 17.55) averted, whereas the deaths averted by MDA would be equivalent to 0.14% of the under-5 population, at a cost of $54.93/DALY averted (95% UI: 31.32, 106.37). MDA to only children 1-5 months old would avert a number of deaths equivalent to 0.11% of the population at a cost of $17.72/DALY averted (95% UI: 9.60, 38.71). In sensitivity analyses, results were most sensitive to the estimated impact of macrolide resistance, baseline mortality rates, AZM efficacy, and the costs of MDA delivery, and were less sensitive to intervention coverage, and risks and costs of adverse events. All strategies were cost-saving if AZM were to lead to ≥5% reductions in hospitalizations. Cost-effectiveness of all strategies decreased with increasing macrolide resistance, with dramatic reductions in cost-effectiveness at extreme prevalences of macrolide resistance (~80%).

Conclusions

Targeting AZM to children at highest risk of death may be an antibiotic-sparing and highly cost-effective, or even cost-saving, strategy to reduce child mortality. However, targeted AZM averts fewer absolute deaths and may not reach all children who would benefit. Any AZM administration decision must consider implications for antibiotic resistance.

INTRODUCTION

Despite dramatic mortality reductions in children under age 5 in recent decades, continued progress is needed to achieve the Sustainable Development Goal targets for child survival.[114,115] Interventions are particularly needed in sub-Saharan Africa (SSA) where child mortality remains disproportionately high.[116]

Empiric azithromycin (AZM) administration may be a promising intervention for reducing under-5 mortality and is being considered for implementation.[117] Trials of mass drug administration (MDA) of AZM for trachoma control reported child mortality benefits in Ethiopia[28] and Niger.[118] These results were confirmed by the recent Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance (MORDOR) Trial, a cluster-randomized trial of bi-annual oral AZM among children 1-59 months of age in 1,533 communities in Niger, Malawi, and Tanzania.[119] The investigators reported a 13.5% reduction in all-cause mortality, with a stronger effect in children 1-5 months of age. Although macrolide resistance in *Escherichia coli* and *Streptococcus pneumoniae* has previously been reported to emerge after AZM MDA, [15,120–123] in MORDOR, the effect of AZM did not appear to wane over time[124] and resistance to other antibiotic classes did not appear to increase.[125]

Strategies targeting AZM to children at highest risk of mortality may limit antibiotic exposure to groups of children most likely to benefit, thus limiting overall drug pressure in the population and reducing macrolide resistance. Several AZM trials are currently ongoing that target high-risk populations, including children recently hospitalized with any infectious condition,[104] neonates,[126] children with severe diarrhea,[29] and children with uncomplicated severe acute malnutrition.[127] However, targeted AZM may not reach all children who stand to benefit, and AZM efficacy is not known in these populations.

If AZM is shown to have significant benefit in reducing mortality in these groups, targeted strategies may be more cost-effective than MDA. In SSA, high child mortality rates combined with limited health resources results in a clear need to maximize health impact with existing resources. Data on the relative cost-effectiveness of these strategies are needed.

We modeled the impact and cost-effectiveness of MDA and targeted AZM interventions to illustrate mortality reduction, consequences of macrolide resistance, and resource implications of these strategies. We modeled the cost-effectiveness of MDA, and considered two examples of targeted AZM interventions - AZM administered at hospital discharge to children 1-59 months old hospitalized for any infectious condition and MDA administered only to children 1-5 months of age. Post-discharge AZM is currently being tested in a clinical trial,[104] and this is an accessible population at high risk of death as well as subsequent re-hospitalization.[128] We considered MDA to community-based children 1-5 months of age as the MORDOR Trial reported highest mortality rates in this age group at all sites. We also modeled the impact of combining MDA with post-discharge AZM for those hospitalized to ensure high coverage of those at highest risk of mortality.

METHODS

Model overview

We constructed a decision tree model using TreeAge Pro software to evaluate the impact and cost-effectiveness of four AZM administration strategies by comparing costs and health effects expected in a 1-year period with and without implementation of these strategies. The interventions considered were as follows: (1) bi-annual MDA of AZM to all children 1-59 months residing in the SSA region ($MDA_{1\text{-}59\ mo}$) (2) bi-annual MDA of AZM to only children 1-5 months of age in SSA ($MDA_{1\text{-}5\ mo}$), (3) AZM administered at hospital discharge to children 1-59 months of age being

discharged from hospitalization for any infectious condition (post-discharge AZM), or (4) bi-annual MDA to all children 1-59 months combined with AZM at discharge for those hospitalized. Model inputs were sourced from published literature whenever possible and with model assumptions when no data were available. Health outcomes in the base-case model included macrolide resistance in *S. pneumoniae* or *E. coli* and death. Sensitivity analyses models also included AZM-related adverse events (AEs) and hospitalizations in addition to macrolide resistance and death. Estimates of AZM efficacy against mortality in all interventions (including post-discharge AZM) were sourced from the MORDOR Trial.[119] Epidemiologic parameters are presented as 1-year cumulative incidence or prevalence if incidence data were not available. Costs were from the payer perspective, and included the cost of the intervention (drug and delivery costs), costs associated with macrolide resistance, and health care utilization costs. The costs of two rounds of MDA were included in the MDA arms for this 1-year time period, and, for the post-discharge AZM, costs of AZM at the index and subsequent hospitalization were included. Cost parameters for MDA were sourced from a study that included up-front costs in estimates per person treated[129] so the cost per person treated for the first and second round were assumed to be the same. All costs were standardized to 2019 United States Dollars (USD) using Consumer Price Indices. Results were expressed in terms of cost per disability-adjusted-life-year (DALY) averted and per death averted in a 1-year period (incremental cost-effectiveness ratios [ICERs]). DALYs were not age-weighted, and neither costs nor outcomes were discounted, given the 1-year time horizon.

Due to the known shortcoming that standard WHO willingness-to-pay (WTP) thresholds (one to three times GDP per capita[130]) are not affordable in practice,[131–133] used the benchmark intervention approach to identify a WTP threshold.[131] In this approach, the intervention ICER is compared to the ICER of an existing intervention that has already been widely implemented in the SSA region, as the benchmark intervention is one for which policymakers are willing and able to pay. We considered the benchmark intervention to be cotrimoxazole prophylaxis for HIV-infected/exposed children in SSA, which is estimated to have an ICER of approximately $50/DALY averted.[134] This benchmark threshold is also comparable to the ICERs of other existing child health interventions that have been implemented in SSA.[135]

Approach to modeling AZM resistance

We considered macrolide resistance to be resistance in either nasopharyngeal S*treptococcus pneumoniae* or enteric *Escherichia coli*. In the base-case model, we assumed, conservatively, that AZM will have no effect on hospitalizations or mortality in children who have developed macrolide resistance. Due to evidence that AZM, like other broad-spectrum antibiotics, may have an effect in the presence of resistance. [136–142] and recent evidence that the efficacy of MDA AZM against mortality does not appear to wane over time with repeated administration,[124] we allow up to a 13.5% reduction in mortality in children with macrolide resistance in sensitivity analyses. Our models assume macrolide resistance prevalence remains constant throughout the 1-year time horizon, though there is evidence of a rapid increased followed by a marked decline in macrolide resistance following AZM exposure[15,143,144] Additionally, our models estimate that children who develop macrolide resistance as a result of AZM treatment will incur extra costs in this 1-year period, due to the potential for increased healthcare costs to treat resistance infections.[145] Thus, in our model, average costs per child treated and population-level efficacy decrease linearly with increasing prevalences of macrolide resistance (Appendix figure 1).

Base-case model

All base-case parameters and their sensitivity ranges are presented in Table 1. The only health effect in the base-case model was reduction in mortality due to AZM. Our base-case model assumes 31% prevalence of macrolide resistance resulting from AZM in all intervention arms, 13.5% efficacy against mortality in 1-59 month old children (for both MDA and post-discharge

cohorts) and 24.9% efficacy against mortality in 1-5 month old children. The base-case model assumes MDA coverage of 90%, as reported in the MORDOR Trial. Post-discharge arm assumes 77.3% coverage, which has been reported to be the proportion of children who died for whom care was sought prior to death.[146] The base-case model assumes no increased risk of AEs due to AZM, as there are data from low- and middle-income countries that suggest AE incidence may be comparable or higher in children not treated with AZM.[118,147–149] In sensitivity analyses we allowed for the possibility of AZM-related AEs.

Sensitivity analyses

We conducted extensive sensitivity analyses to evaluate the robustness of our results against parameter uncertainty. All model parameters were varied in sensitivity analyses: efficacy against mortality, baseline mortality rates, prevalence of macrolide resistance, efficacy against mortality among those with macrolide resistance, cost of AZM drugs, cost of drug delivery, costs associated with macrolide resistance, intervention coverage, efficacy against hospitalizations, efficacy against hospitalization among those with macrolide resistance, cost of hospitalizations, prevalence of hospitalizations, risk of AE, proportion of AEs that result in an outpatient visit, cost of an outpatient visit, disability weights for AEs and hospitalizations, and years of life lost per death (Table 1). We conducted one-way sensitivity analyses to identify parameters that have the largest influence on results, and present the ICER changing one variable at a time while keeping all others constant. We also conducted threshold analyses to identify the minimum efficacy against mortality that post-discharge AZM would have to demonstrate to be as cost-effective as the base-case MDA strategies, as well as the threshold baseline mortality rate, threshold macrolide resistance prevalence, and threshold mortality efficacy at which each strategy would be no longer cost-effective. Sensitivity ranges for deterministic analyses were informed by the low and high estimates reported in relevant literature, scientifically plausible ranges where data are not available, or, in the case of the efficacy estimates, the confidence interval range of MORDOR Trial efficacy estimates.

We conducted probabilistic sensitivity analyses to illustrate results in many simulated scenarios varying all parameters simultaneously. We specified beta distributions for probability parameters, gamma distributions for costs, and lognormal distributions for relative risks. When alpha and beta parameters could not be estimated from published data, method of moments was used to estimate alpha and beta given the mean and standard error. When no standard error estimates could be estimated from published data, we assumed standard error to be 20% of the mean. We conducted 10,000 Monte Carlo simulations to achieve adequate convergence[150] and applied the WTP threshold of $50/DALY averted. The ICER at the 2.5th percentile and the 97.5th percentile were taken to form the 95% uncertainty interval (95% UI) for the base-case estimate.

We also conducted an exploratory analysis evaluating cost-effectiveness if AZM were to avert healthcare costs by reducing hospitalization rates. This sensitivity analysis includes effects of AZM on AZM-related adverse events and efficacy against hospitalizations, and the healthcare utilization costs of AEs and hospitalization. While there is limited evidence of reductions in hospitalizations due to AZM, this intervention may prevent or treat infectious conditions that are common causes of pediatric hospitalizations in SSA.

RESULTS

Mortality results

We estimate that $MDA_{1\text{-}59\ mo}$ at 90% coverage would avert approximately 19.7 million DALYs and 230,000 deaths in a 1-year period, at a cost of $54.93 (95% UI: 31.32, 106.37) per DALY averted (Table 2a and 2b). These averted deaths are approximately equivalent to 0.14% of the population

of children under age 5 in SSA (Figure 2). Targeting MDA to children 1-5 months old at 90% coverage would avert approximately 16.3 million DALYs and 185,000 deaths (approximately 0.11% of the population the under-5 population) at a cost of $17.72 (95% UI: $9.60, 38.71) per DALY averted. Targeting AZM to children at hospital discharge would avert approximately 3.2 million DALYs and 37,000 deaths at a cost of $9.00 (95% UI: 4.78, 17.55) per DALY averted. Given there is evidence that the majority of children who died had sought care prior to death,[146,151] we also present estimates of deaths averted by post-discharge AZM if 75% of community-based children who die sought care prior to death (Figure 2). Adding post-discharge AZM to MDA averted approximately 900,000 additional DALYs and 10,000 deaths than MDA alone, at a cost of $57.03 (95% UI: 31.87, 109.89) per DALY averted. ICERs estimated by the deterministic model were lower for all strategies (Table 2a). Number needed to treat (NNT) to avert one death in targeted strategies were at least half that of $MDA_{1\text{-}59\ mo}$ strategies. Table 3a presents baseline mortality rates at which AZM to achieve various absolute reductions in mortality, at varying relative mortality reduction effect sizes (applicable to all strategies). At the 13.5% reduction in mortality reported in MORDOR, the intervention would avert 2.5 deaths per 1,000 child-years in a population with baseline 18.5 deaths per 1,000 child-years, and 5.0 deaths per 1,000 child-years in a population with baseline 37.0 deaths per 1,000 child-years.

All strategies were highly sensitive to macrolide resistance prevalence, with the base-case assumption of no effect in children with resistance (Figure 3). Threshold analyses identified the macrolide resistance prevalence at which each intervention would no longer be cost-effective at a WTP of $50 as ≥55.6% for $MDA_{1\text{-}59\ mo}$, ≥87.6% for $MDA_{1\text{-}5\ mo}$, ≥56.7% for $MDA_{1\text{-}59\ mo}$ and post-discharge AZM, and ≥92.1% for post-discharge AZM. Costs per DALY averted increase for all interventions at increasing prevalences of macrolide resistance (Table 4 and Figure 4), with dramatic increases at extreme prevalences of resistance (>80%). Increasing macrolide resistance to 75% from the 31% in the base-case model corresponded to approximately 200% increases in the ICERs for all interventions. NNT increased in a similar pattern.

All strategies were also highly sensitive to efficacy of AZM against mortality. Threshold analyses suggest the minimum efficacy against mortality that AZM would have to demonstrate to be considered cost-effective (at a WTP threshold of $50 and base-case mortality rates) is 8.5% in the $MDA_{1\text{-}59\ mo}$ strategy, 5.6% in the $MDA_{1\text{-}59\ mo}$ + post-discharge strategy, 3.1% in the $MDA_{1\text{-}5\ mo}$ strategy, and 1.4% in the post-discharge strategy. Results were also highly influenced by baseline mortality rates. Higher baseline mortality rates substantially reduced the ICER in all interventions, and lower baseline mortality rates substantially increased it (Table 4). The threshold baseline mortality rates at which each intervention would no longer be cost-effective, at various efficacies against mortality and WTP thresholds, are presented in Table 3b.

Costs of MDA delivery were also highly influential for the MDA interventions. Probability and costs of AEs made negligible difference on ICERs for any intervention, nor did additional costs incurred by children with macrolide resistance.

All strategies were cost-saving in one-way sensitivity analyses in which AZM resulted in at least a moderate reduction in hospitalizations (Table 4). Threshold analyses suggest post-discharge AZM would be cost-saving if it demonstrated an efficacy against hospitalizations as little as 1.1%, at the base-case prevalence of hospitalization. All MDA strategies would be cost-saving with ≥6.1% reduction in hospitalization at the base-case prevalence of hospitalization. In a two-way sensitivity analysis of the simultaneous efficacy of AZM against hospitalization and underlying prevalence of hospitalization, all interventions were cost-saving in the majority of scenarios, (Figure 4) but post-discharge AZM was cost-saving in a higher proportion of sensitivity scenarios than the MDA strategies. Additionally, post-discharge AZM was cost-saving more frequently in

the probabilistic models, such that the mean and median ICERs were cost-saving for post-discharge AZM (Appendix Figures 2 and 3).

Probabilistic sensitivity analyses

Scatterplots in Figure 5 depict the incremental costs and effects resulting from the 10,000 Monte Carlo simulations. $MDA_{1\text{-}5\ mo}$ had the widest variability in DALYs averted. The strategies targeting high mortality children (post-discharge AZM and $MDA_{1\text{-}5\ mo}$) were below the WTP threshold of $50 for all or nearly all simulations. Cost-effectiveness acceptability curves depicted in Figure 6 suggest the targeted strategies are more likely to be cost-effective at lower WTP thresholds than $MDA_{1\text{-}59\ mo}$.

DISCUSSION

In this cost-effectiveness modeling analysis, all AZM administration strategies tested were cost-effective for preventing child mortality, with strategies targeting higher mortality risk populations most cost-effective. The impact of increasing prevalences of macrolide resistance (with presumed diminished efficacy) and in exploratory analyses in which AZM prevents hospitalization, thus averting healthcare costs, have also been tested in this analysis.

Our results are comparable to other data on cost-effectiveness of mass distribution of AZM for trachoma in LMICs[152] and are also comparable to the cost-effectiveness of other child health interventions considered by Disease Control Priorities Network as highly cost-effective,[135] including parenteral artesunate for severe malaria ($4/DALY averted),[153] insecticide-treated mosquito nets ($4-44/DALY averted)[154–156], and vaccines for rotavirus ($10-38/DALY averted)[157,158] and measles ($5/DALY averted).[159]

Targeting high-mortality groups (hospitalized children post-discharge, and community-based children under 6 months of age) appears much more cost-effective than providing MDA to all under-5 children. Other health interventions that target high-risk groups have been reported to be more cost-effective than universal administration, such as cardiovascular disease screening,[160] rotavirus vaccination in high-income countries,[161] and AZM for trachoma control.[16] Targeting AZM to high-mortality populations may be a useful strategy to maximize the health impact of limited health budgets while also minimizing antibiotic exposure. Evidence of stronger effect sizes of AZM MDA at higher rates of baseline mortality were reported in MORDOR,[162] which also suggests that there may be increased cost-effectiveness in high-mortality populations.

However, the assumption that AZM has the same or greater effect size when targeted to higher risk populations has not yet been demonstrated in robust clinical trials. If there are indirect effects of AZM that are realized with community-wide delivery, such as reduced pathogen carriage and transmission, this benefit would be lost with a more targeted approach. However, the mechanisms of effect for MDA, and the role of indirect benefit, are unclear, and there are data that suggest no indirect effects of MDA of AZM.[163] In addition, targeted approaches may not reach all children who would benefit, so may be ethical implications to consider.[164] In this analysis, a targeted approach was highly cost-effective, even when the effect size was as small as a 1.4% reduction in mortality. Current RCTs testing targeted approaches are unlikely to be powered to detect an effect of this magnitude and thus run being underpowered for magnitudes of effect that would actually be cost-effective when compared to MDA.

Although targeted approaches appeared more cost-effective in this analysis, MDA to community-based children 1-59 months old would still be considered highly cost-effective. Additionally, hospital-based interventions, such as post-discharge AZM, may not reach all children who stand

to benefit, including children who die in hospital. Barriers to care-seeking such as travel distance and costs of care[165–168] may particularly affect impoverished families and those living in rural areas, populations who are also at high risk of child mortality.[169–171] MDA platforms are highly equitable, and are particularly well-suited to reduce burden of disease among impoverished populations.[172] Even so, MDA programs are not without challenges, including difficulties in achieving high coverage. Coverage rates of MDA programs in practice (often well below the coverage target of 80%[173]) are comparable to reported rates of care-seeking for sick children prior to death.[146,151] Depending on care-seeking, hospital-based interventions might still reach the majority of children during a high-risk period at risk for death.

The rate of increase in population-level antibiotic resistance rates have been estimated to depend on the proportion of a population that is exposed to the antibiotic.[174] While the cost-effectiveness of all strategies in our model decreased with increasing macrolide resistance prevalence, the decrease was most pronounced in MDA. However, it is possible that AZM may continue to be at least somewhat effective at preventing child mortality even with widespread macrolide resistance. Long term courses of cotrimoxazole prophylaxis are widely used in SSA, but still lead to improved outcomes in areas of high cotrimoxazole resistance.[175,176] In MORDOR, there was no evidence that the mortality benefit waned with continued MDA of AZM in Niger[124] and waning would be expected if increasing AZM resistance were resulting in untreated infections. If any AZM interventions were to be implemented, continued antimicrobial resistance surveillance, as is being done with trachoma control programs, will be important for monitoring effectiveness of the program and making decisions about cessation.

We estimate that if AZM were to have even a small impact in reducing hospitalization rates in any of the strategies, the intervention is likely to be cost-saving, resulting in improved health outcomes at a reduced cost to the payer. The impact of these cost-saving is somewhat dependent on how health care costs are borne, and may not have a big impact to the payer if costs are borne by the payee. We found post-discharge AZM was more likely to be cost-saving than MDA in sensitivity scenarios, due to the higher hospitalization rates in post-discharge children.[4–6,177] While there is no trial evidence of AZM reducing hospitalizations, the biological mechanism of AZM's effect has been hypothesized to be prevention or early treatment of respiratory infections, malaria, and diarrhea,[178] which are common causes of pediatric hospitalizations. In addition, there is evidence that AZM reduces clinic visits due to gastrointestinal infections, upper respiratory tract infections, and nonmalarial fevers,[124] though this study reported no difference in hospital admissions due to the addition of azithromycin to malaria chemoprevention. Other antibiotic interventions have also been reported to prevent hospitalizations, including cotrimoxazole in HIV-affected children[179,180] and amoxicillin in severe acutely malnourished children.[181] Trials of AZM or other antibiotics should consider ascertaining hospitalizations in study participants in order to capture potential cost-saving effects.

We have conducted extensive sensitivity analyses to evaluate the robustness of our results and presented results varying each input across a wide plausible range of values. Even so, there are limitations in our approach and assumptions. First, trial evidence for the efficacy of post-discharge AZM is not yet available at the time of this writing, and we have made assumptions about the efficacy of this strategy. While the magnitude of benefit observed in the 1-5 month old age group in MORDOR was greatest, the study was not designed or powered to explicitly evaluate impact in this group and the estimate may be unstable. Additionally, the baseline mortality rates observed in MORDOR were lower than the trial investigators had expected, which may affect our estimates. We varied baseline mortality rates in sensitivity analyses to present results under different mortality rates. Additionally, we did not explicitly account for the impact of economies of scale in our model of MDA, which may have an important impact in economic evaluations of MDA.[182] We

modeled efficacy based on results of a single trial; although there was significant variability in the effect size observed between sites in this trial. However, this trial was the largest and most recent of the MDA trials, and the overall effect was statistically significant. In addition, a recent meta-analysis of all MDA trials has also reported a statistically significant benefit.[183] Finally, we assumed this intention-to-treat effectiveness estimate to approximate effectiveness in children who are actually treated (ie as-treated analysis), so we may have underestimated the effectiveness, and cost-effectiveness, of AZM in all arms. While we have employed a conservative approach to capturing the effects of macrolide resistance, we are neither able to estimate future effects on costs or health outcomes due to macrolide resistance created by this intervention, nor negative externality effects, such as the likelihood of macrolide resistance transmitted to household or community members who did not receive the intervention themselves. Additionally, our models assume children with macrolide resistance may incur additional costs, but this may not be sufficient to capture the true costs of macrolide resistance, a limitation of all economic evaluations of antibiotic interventions.[184,185] We also did not capture costs from the societal perspective. This perspective would be particularly important if AZM were to avert hospitalizations, as pediatric hospitalizations often lead to catastrophically high costs to the children's families.[186,187] We also did not capture potential indirect benefits if AZM were to reduce carriage and transmission of pathogen, nor any effects of the antibiotic in improving child nutritional status.

CONCLUSION

AZM administration is likely to be a highly cost-effective, or potentially even a cost-saving, strategy for reducing child mortality in SSA even in the presence of macrolide resistance. Targeting antibiotic administration to high-mortality groups would likely be antibiotic sparing and may be a particularly cost-effective strategy to maximize potential benefit while minimizing costs and antibiotic exposure. Trial evidence of post-discharge AZM and other targeted approaches is needed, and models will be updated when such data become available. Policymakers should consider implications for resistance as well as equity concerns that targeted strategies may not reach all who stand to benefit.

TABLES AND FIGURES

Table 1. Model parameters for deterministic and probabilistic models of cost-effectiveness of azithromycin administration strategies for reducing child mortality in sub-Saharan Africa

Parameter	Base case value (sensitivity range)	Parameters for probabilistic analysis		Notes and key assumptions	Source
		Standard error or parameters	Distribution		
Coverage					
Proportion of population reached by post-discharge AZM	77.3% (65%, 93%)	α=399, β=117	Beta	Proportion of deaths that sought care prior to the death	146,151
Proportion of population reached by MDA	90% (60%, 95%)	0.106	Beta	Assumed to be the same in 1-5 month old and 1-59 month old cohorts	31,188–191
Antimicrobial resistance					
Proportion of children receiving AZM who develop macrolide resistance	31.0% (10.0%, 95.0%)	α=83, β=235	Beta	Assumes 6-month resistance (midpoint) is constant throughout. Assumed to be the same in post-discharge vs MDA cohort	15,120
Adverse Event					
Proportion of children who receive AZM who experience an adverse event	0% (0%, 10%)	α=232, β=2423	Beta	Assumed to be the same in post-discharge and MDA children	148,192–194
Proportion of children who experience an AE who seek outpatient care	25.0% (15.0%, 40.0%)	0.05	Beta	Model assumption, as AEs are mild. AEs are assumed to lead to no increased risk of hospitalization or death. SE is assumed to be 20% of base case.	192, model assumption
Hospitalization					
Proportion who are hospitalized in community cohort	7.0% (1.9%, 10.0%)	α=175, β=2327	Beta		5,177,195
Proportion who are re-hospitalized among post-discharge cohort	17.7% (11.6%, 24.0%)	α=1820, β=8457	Beta		5,6,177
RR of hospitalization associated with AZM treatment	1 (0.75, 1)	μ=-0.145, σ=0.0365	Lognormal	Assumed to be the same in post-discharge and MDA cohorts	180,181,196; model assumption
RR of re-hospitalization associated with AZM treatment among children with AMR	1.0 (0.9, 1.0)	μ=0, σ=0.0268	Lognormal	Assumed to be the same in post-discharge and MDA cohorts	Model assumption
Mortality					
Baseline mortality proportion in post-discharge children	4.4% (2.1%, 12.0%)	α=535, β=11055	Beta		5,6,197–204

Baseline mortality proportion in community-based children (1-59 months)	1.64% (0.39%, 3.2%)	α=1538, β=91653	Beta		[5,119,177]
Baseline mortality proportion in 1-5 month old community-based children	3.1% (2.0%, 3.9%)	α=637, β=22575	Beta		[119]
RR of mortality associated with MDA AZM treatment in community children	0.865 (0.802, 0.933)	μ= -0.145, σ=0.0365	Lognormal	Assumed to the same in MDA (1-59 month) and post-discharge cohorts	[119], model assumption
RR of mortality associated with AZM treatment in post-discharge children	0.865 (0.75, 0.99)	μ= -0.145, σ=0.0365	Lognormal	Base case assumed to be the same efficacy as demonstrated MDA efficacy	[119], model assumption
RR of mortality associated with AZM treatment in 1-5 mo olds	0.751 (0.63, 0.894)	μ= -0.286, σ=0.089	Lognormal		[119]
RR of mortality associated with AZM treatment in children with AMR	1.0* (0.9, 1.0)	μ=0, σ=0.0268	Lognormal	Assumed to be the same in post-discharge and MDA cohorts	Model assumption
Years of Life Lost					
Among 1-59 month age group	85.51 (82.01, 87.01)	0.4	Normal	Assumes a mean age at death of 18 months	[3,205,206]
Among 1-5 month age group	87.64 (87.39, 87.89)	0.05	Normal	Assumes a mean age at death of 3 months	Model assumption
Life expectancy (1-59 month age group)	87.007248			Global Burden of Disease reference life table, age at death 1 year	[207]
Life expectancy (1-5 month age group)	87.885872			Global Burden of Disease reference life table, age at death 0 years	[207]
Years Lived with Disability					
Size of community-based cohort (1-59 months)	167,768,444			UN Population Division estimate of children under-5 in SSA for 2018	[208]
Size of community-based cohort (1-5 months)	38,600,000			UN Population Division estimate of live births in SSA in 2018	[208]
Size of post-discharge cohort	11,743,791			The product of the number of children in SSA and prevalence of hospitalization	[5]
Duration of hospitalization	5 days (3,10)	1	Normal	SE assumed to be 20%	[209–212]
Duration of adverse event	3 days (1,5)	0.6	Normal	SE assumed to be 20%	Model assumption
Disability weights					

Hospitalization/re-hospitalization	0.133 (0.088, 0.19)	0.026	Beta	GBD disability weights for health state “infectious disease – acute episode, severe”	[213]
Adverse event	0.006 (0.002, 0.012)	0.003	Beta	GBD disability weights for health state “infectious disease – acute episode, mild”	[213]
Co-morbidity adjustment	None			The model assumes no co-occurring health states. Hospitalizations and AEs are assumed to not overlap due to the short duration of both events.	Model assumption
Costs					
Oral azithromycin	$0.97, ($0.59, $1.56)	0.194	Gamma		[214]
Hospitalization	$976.84 ($90.18, $5328.85)	195.37	Gamma	Average of inpatient costs in SSA	[195]
Outpatient visit	$21.97 ($2.07, $122.31)	4.39	Gamma	Average of outpatient costs in SSA	[195]
Delivery of MDA per person treated	$0.54 ($0, $9.15)	0.11	Gamma		[129]
Delivery of post-discharge AZM per person treated	$0 ($0, $1)	0.40	Gamma	Assumed to be included with existing post-discharge care, and to incur no additional costs of delivery. Sensitivity range is informed by service delivery cost from other hospital-based interventions in SSA	[215,216], model assumption
Macrolide resistance per AZM course	$0.32 ($0, $0.85)	0.06	Gamma		[145]

Standard error estimates for gamma distributions are assumed to be 20% of the mean for all costs

Table 2 impact and cost-effectiveness of azithromycin administration strategies for reducing child mortality in sub-Saharan Africa

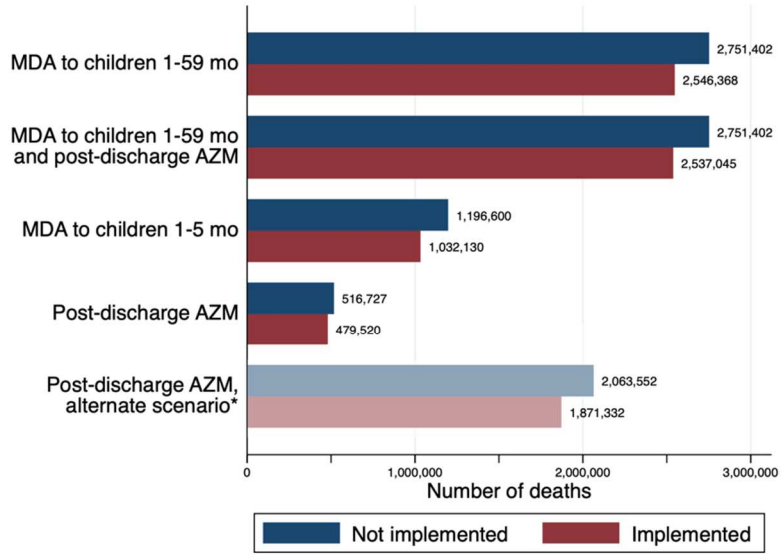
2a. Deterministic model results

	Number exposed to AZM	Total cost of adding intervention	Total DALYs averted	ICER ($/DALY averted)	DALYs averted by spending $1 million	Total deaths averted	ICER ($/death averted)	Deaths averted by spending $1 million	NNT
MDA to children 1-59 mo	150,991,600	$448,173,265.93	19,724,064	22.72	44,010	230,665	1942.96	515	727
MDA to children 1-59 mo + post-discharge AZM	150,991,600	$455,871,886.70	20,620,875	22.11	45,234	241,152	1890.39	529	696
MDA to children 1-5 mo	34,740,000	$103,115,268.00	16,264,301	6.34	157,729	185,029	557.29	1,794	209
Post-discharge AZM	129,181,702	$10,808,836.25	3,181,561	3.40	294,348	37,204	290.53	3,442	316

2b. Probabilistic model results

	ICER ($/DALY averted)			ICER ($/death averted)		
	Median	Mean	95% UI	Median	Mean	95% UI
MDA to children 1-59 mo	50.53	54.93	31.32, 106.37	2929.23	3180.53	1855.69, 5907.04
MDA to children 1-59 mo + post-discharge AZM	51.50	57.03	31.87, 109.89	3022.46	3303.47	1870.63, 6346.19
MDA to children 1-5 mo	15.80	17.72	9.60, 38.71	1091.61	961.03	585.78, 2347.47
Post-discharge AZM	8.29	9.00	4.78, 17.55	488.66	528.93	281.27, 1034.28

Abbreviations: AMR = antimicrobial resistance; MDA = mass drug administration; AZM = azithromycin; DALY = disability-adjusted-life-year; ICER = incremental cost-effectiveness ratio; NNT = number needed to treat to prevent one death, 95% UI = 95% uncertainty interval



*If 75% of community-based children who die were hospitalized prior to death, 100% of whom would receive post-discharge AZM. Base-case estimates assume 7% of the population is hospitalized, 4.4% of whom will die without AZM.

Figure 2. Absolute numbers of deaths expected in the relevant populations if each intervention were to be implemented vs not implemented

Table 3a. Impact of AZM on child mortality under various epidemiologic settings
Baseline mortality rates are presented as deaths per 1,000 child-years

Relative mortality reduction	**Threshold baseline mortality rates to achieve absolute mortality reductions of:**			
	2.0 deaths per 1,000 child-years	2.5 deaths per 1,000 child-years	5.0 deaths per 1,000 child-years	10.0 deaths per 1,000 child-years
10%	20.0	25.0	50.0	100.0
13.5%	14.8	18.5	37.0	74.1
20%	10.0	12.5	25.0	50.0
24.9%	8.0	10.0	20.1	40.2

Table 3b. Cost-effectiveness of AZM under various epidemiologic settings
Baseline mortality rates are presented as deaths per 1,000 child-years

Relative mortality reduction	**Threshold baseline mortality rates at which AZM interventions costs would surpass:**	
	$50/DALY averted	$100/DALY averted
MDA (all strategies)		
10%	10.1	5.0
13.5%	7.5	3.7
20%	5.0	2.5
24.9%	3.9	2.0
Post-discharge		
10%	4.0	2.0
13.5%	14.0	1.5
20%	2.0	1.0
24.9%	1.6	0.8

Note: MORDOR Trial reported an absolute mortality reduction of 1.8 deaths per 1,000 child-years, with a relative mortality reduction of 13.5%, in the 1-59 month age group, and an absolute mortality reduction of 4.8 deaths per 1,000 child-years with a relative mortality reduction of 24.9% in the 1-5 month age group.

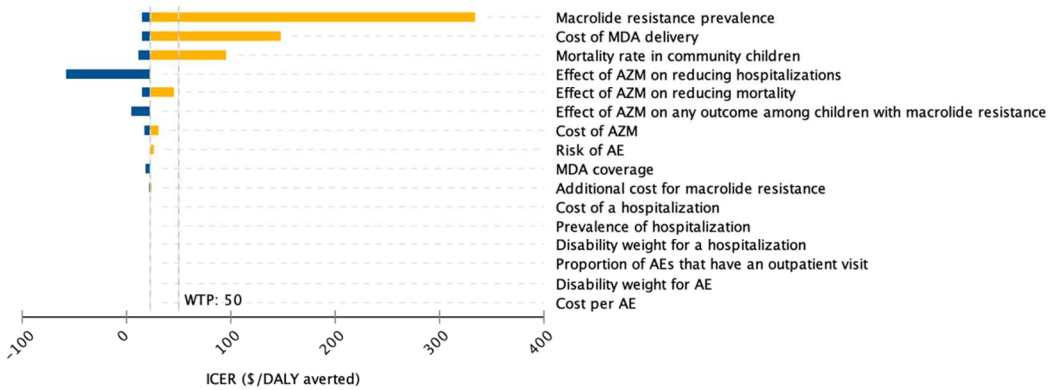
Table 4. One-way sensitivity analyses of the effect of varying each model parameter on results for cost-effectiveness of AZM administration strategies for reducing child mortality in sub-Saharan Africa

Abbreviations: MDA = mass drug administration; AZM = azithromycin; DALY = disability-adjusted-life-year; ICER = incremental cost-effectiveness ratio, mo= months

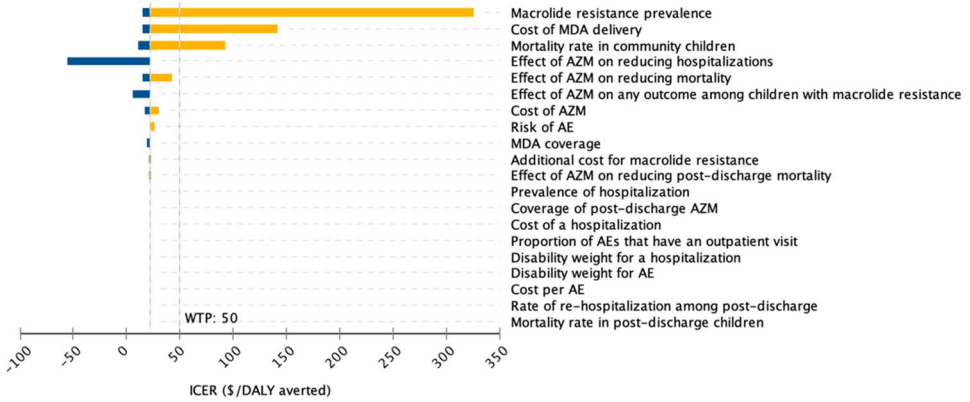
	MDA to 1-59 mo			MDA + post-discharge			MDA to 1-5 mo			Post-discharge		
	Value	Cost per DALY averted	Change in ICER, %	Value	Cost per DALY averted	Change in ICER, %	Value	Cost per DALY averted	Change in ICER, %	Value	Cost per DALY averted	Change in ICER, %
Effectiveness against mortality, relative risk												
Low	0.802	15.49	-31.8%	0.802	15.32	-30.7%	0.63	4.27	-32.6%	0.75	1.83	-46.2%
Base case	0.865	22.72		0.865	22.11		0.751	6.34		0.865	3.4	
High	0.933	45.78	101.5%	0.933	42.38	91.7%	0.894	14.83	133.9%	0.95	7.91	132.6%
Effectiveness against hospitalization, relative risk												
Base case	1	22.72		1	22.11		1	6.34		1	3.4	
Low	0.77	Cost-saving		0.77	Cost-saving		0.77	Cost-saving		0.77	Cost-saving	
Moderate	0.865	Cost-saving		0.865	Cost-saving		0.865	Cost-saving		0.865	Cost-saving	
High	0.95	2.55	-88.8%	0.95	2.8	-87.3%	0.95	0.71	-88.8%	0.95	Cost-saving	
Prevalence of hospitalization, assuming a 10% reduction associated with AZM												
Low	0.019	13.02		0.019	12.98		0.019	3.64		0.05	Cost-saving	
Moderate	0.07	Cost-saving		0.07	Cost-saving		0.07	Cost-saving		0.17	Cost-saving	
High	0.1	Cost-saving		0.1	Cost-saving		0.1	Cost-saving		0.24	Cost-saving	
Baseline mortality rate												
Low	0.0039	95.55	320.6%	0.0039	92.96	320.4%	0.02	9.83	55.0%	0.021	7.12	109.4%
Base case	0.0165	22.72		0.0165	22.11		0.031	6.34		0.044	3.4	
High	0.033	11.65	-48.7%	0.033	11.33	-48.8%	0.039	4.37	-31.1%	0.13	1.25	-63.2%
Macrolide resistance prevalence												
Low	0.15	18.172	-20.0%	0.15	17.69	-20.0%	0.15	5.08	-19.9%	0.15	2.65	-22.1%
Base case	0.31	22.72		0.31	22.11		0.31	6.34		0.31	3.4	
High	0.5	32.24	41.9%	0.5	31.33	41.7%	0.5	8.96	41.3%	0.5	4.97	46.2%
Very high	0.75	65.82	189.7%	0.75	63.99	189.4%	0.75	18.06	184.9%	0.75	10.51	209.1%
Efficacy against mortality in children with macrolide resistance, relative risk												
No reduction in effect	0.865	15.68	-31.0%	0.865	15.46		0.751	4.38	-30.9%	0.865	2.34	-31.2%
Moderately reduced effect	0.93	18.55	-18.4%	0.93	18.2		0.85	5.7	-10.1%	0.93	2.77	-18.5%
Base-case	1	22.72		1	22.11		1	6.34	0.0%	1	3.4	

Cost of AZM drug												
Low	0.59	17.2	-24.3%	0.59	16.67	-24.6%	0.59	4.8	-24.3%	0.59	2.18	-35.9%
Base case	0.97	22.72		0.97	22.11		0.97	6.34		0.97	3.4	
High	1.56	31.3	37.8%	1.56	30.54	38.1%	1.56	8.73	37.7%	1.56	5.29	55.6%
Cost of AZM delivery												
Low	0	14.87	-34.6%	0	14.59	-34.0%	0	4.15	52.8%	--		
Base case	0.5	22.72		0.5	22.11		0.5	6.34		0	3.4	
High	4.58	81.41	258.3%	4.58	78.24	253.9%	4.58	22.72	258.4%	0.5	5	47.1%
Very high	9.15	147.95	551.2%	9.15	141.89	541.7%	9.15	41.28	551.1%	1	6.61	94.4%
Cost of post-discharge AZM delivery												
Base case				0	22.11							
Moderate				0.5	22.3	0.8%						
High				1	22.49	1.7%						
Effectiveness against mortality in post-discharge children, relative risk												
Low				0.75	21.32	3.6%						
Base case				0.865	22.11							
High				0.95	22.67	2.5%						

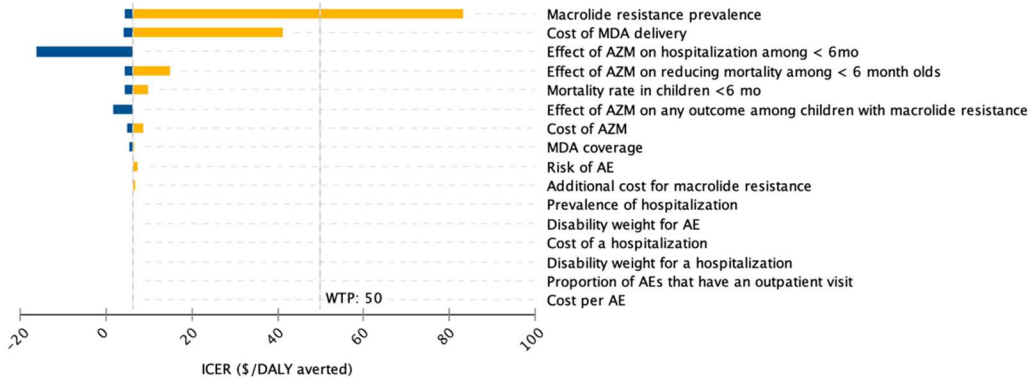
MDA to children 1-59 mo



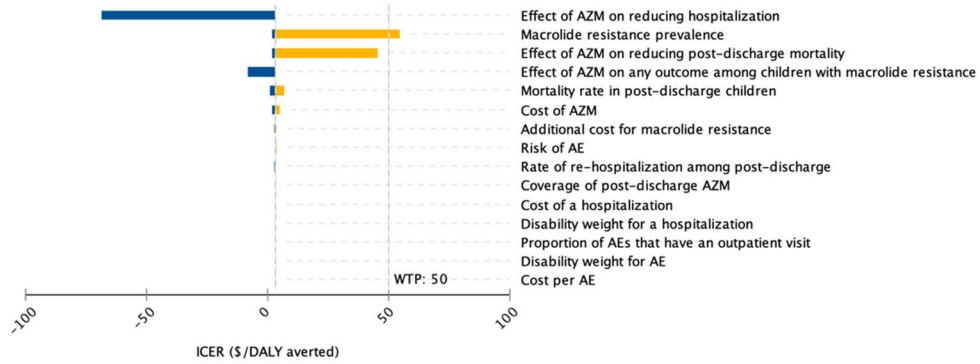
MDA to children 1-59 months + post-discharge AZM



MDA to children 1-5 mo



Post-discharge AZM



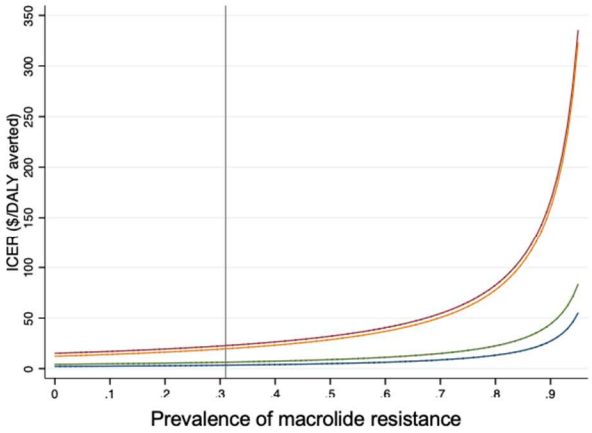
Legend

More cost-effective than base-case
Less cost-effective than base-case

Figure 3. Tornado diagrams of factors which have the greatest influence on results of cost-effectiveness of AZM strategies for reducing child mortality in sub-Saharan Africa

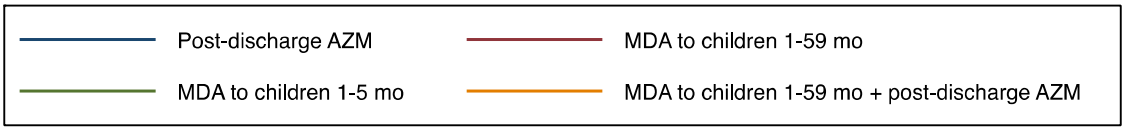
Abbreviations: AZM = azithromycin, MDA = mass drug administration, AE= adverse event, mo = months
Note: Costs per DALY averted < 0 reflect cost-saving strategies which result in improved health outcomes at reduced costs

a. ICER at increasing prevalences of macrolide resistance



b. Percent increase in ICER at increasing prevalences of macrolide resistance

Drop lines indicate macrolide resistance prevalences which approximately correspond to 100, 200, and 500% increases in ICER



increasing prevalences of macrolide resistance

Abbreviations: ICER = incremental cost-effectiveness ratio, MDA = mass drug administration, mo = months, AZM = azithromycin, DALY = disability-adjusted-life-year

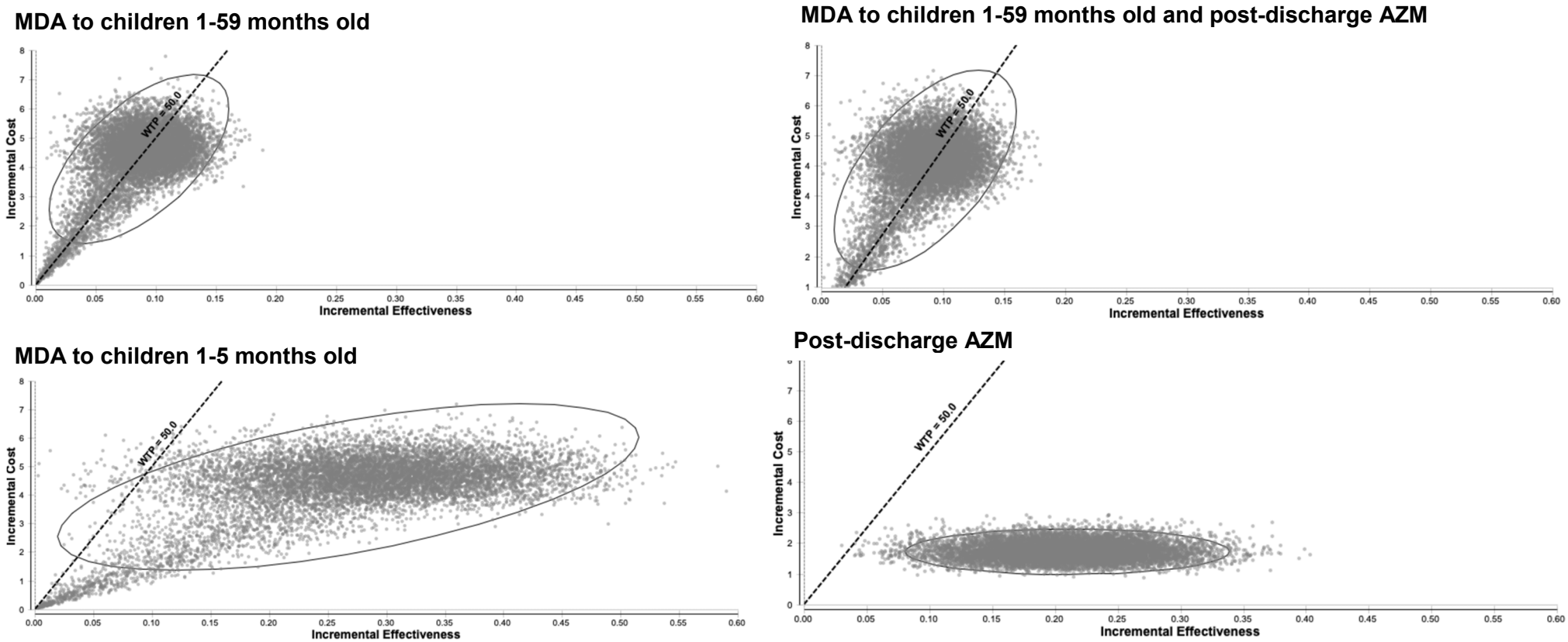


Figure 5. Scatter plots of results from probabilistic sensitivity analyses

Ellipses represent 95% uncertainty interval, Diagonal lines represent willingness-to-pay threshold ($50/DALY averted). Incremental effectiveness refers to DALYs averted.
Abbreviations: MDA = mass drug administration, WTP = willingness-to-pay, AZM = azithromycin

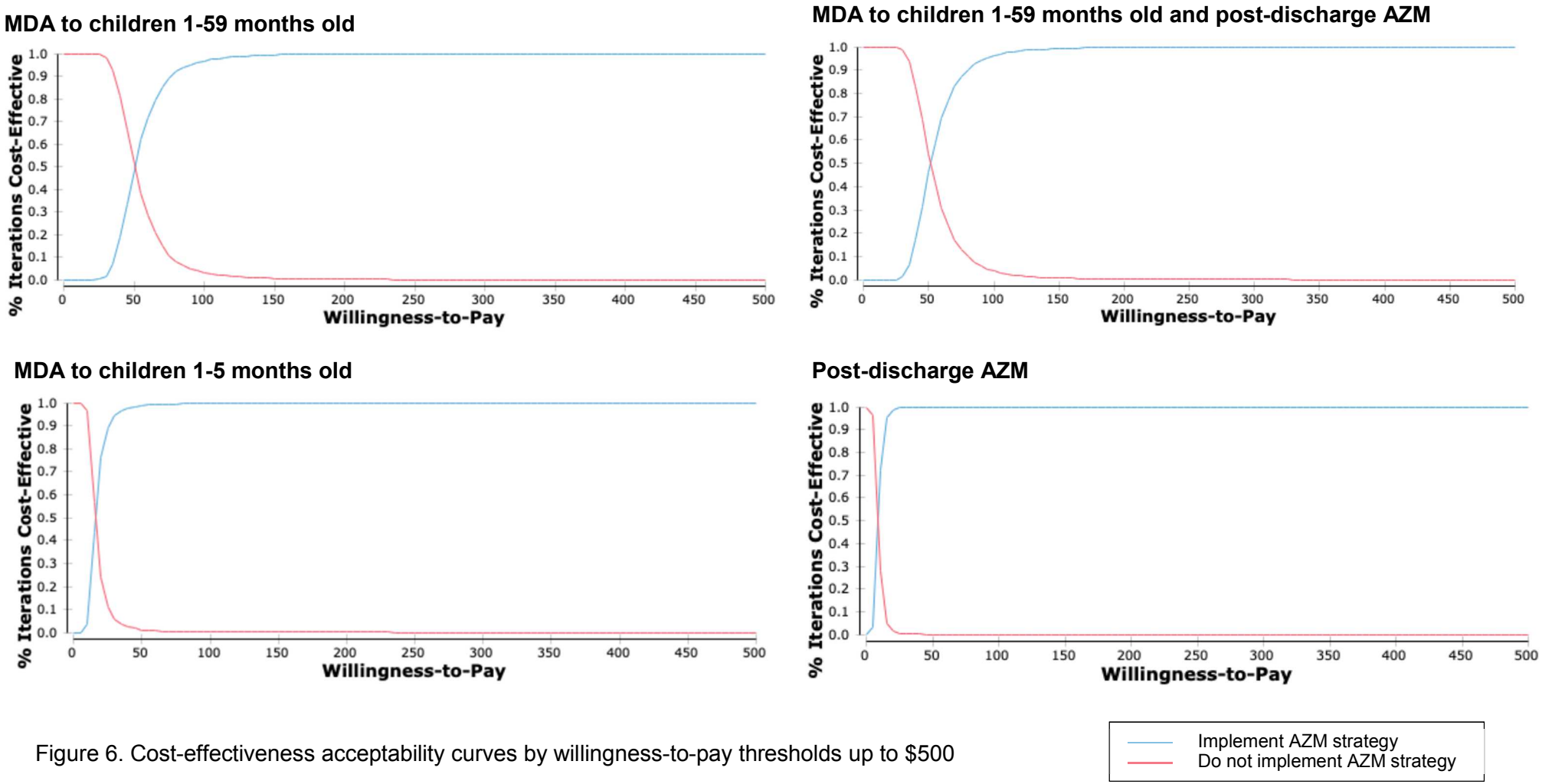
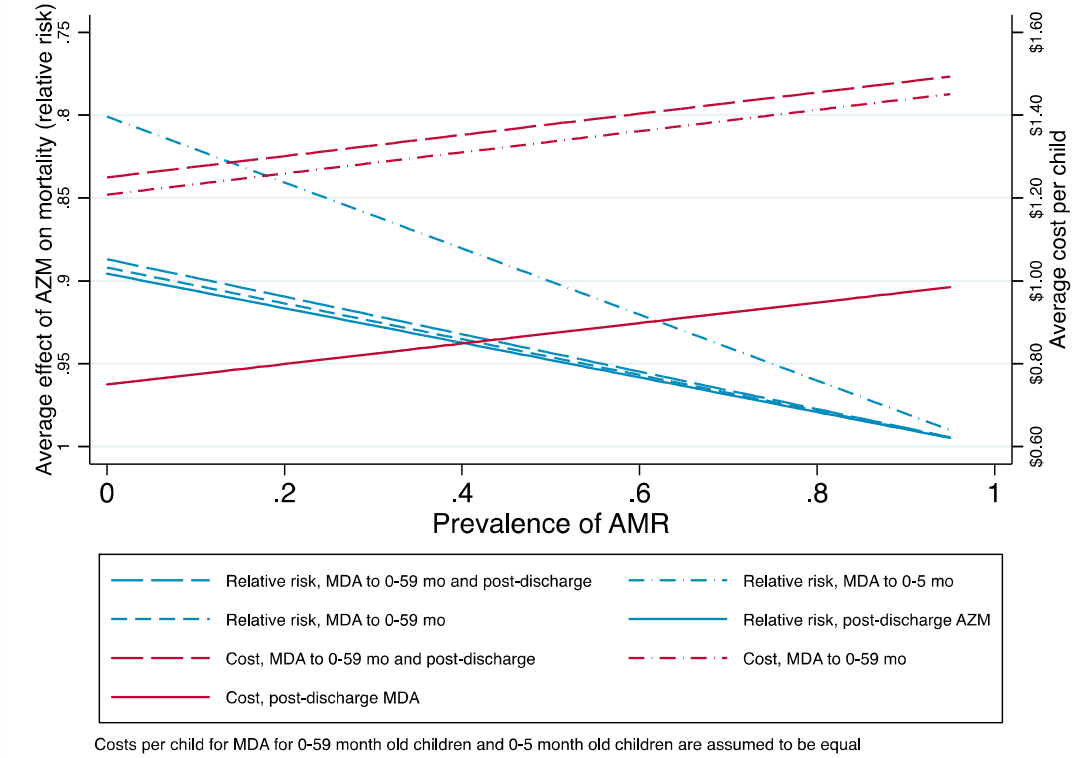
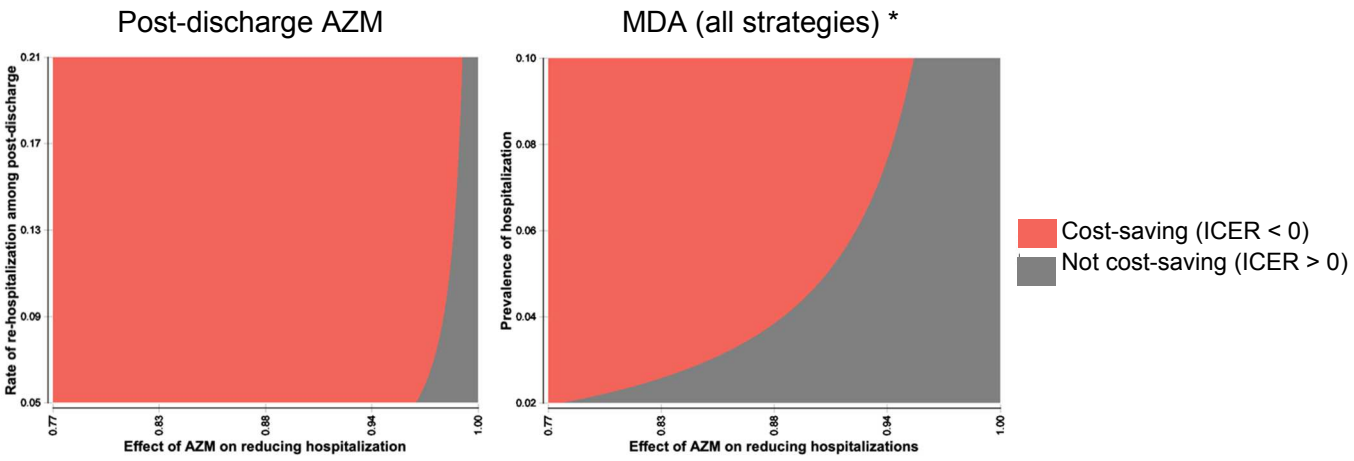


Figure 6. Cost-effectiveness acceptability curves by willingness-to-pay thresholds up to $500

APPENDIX

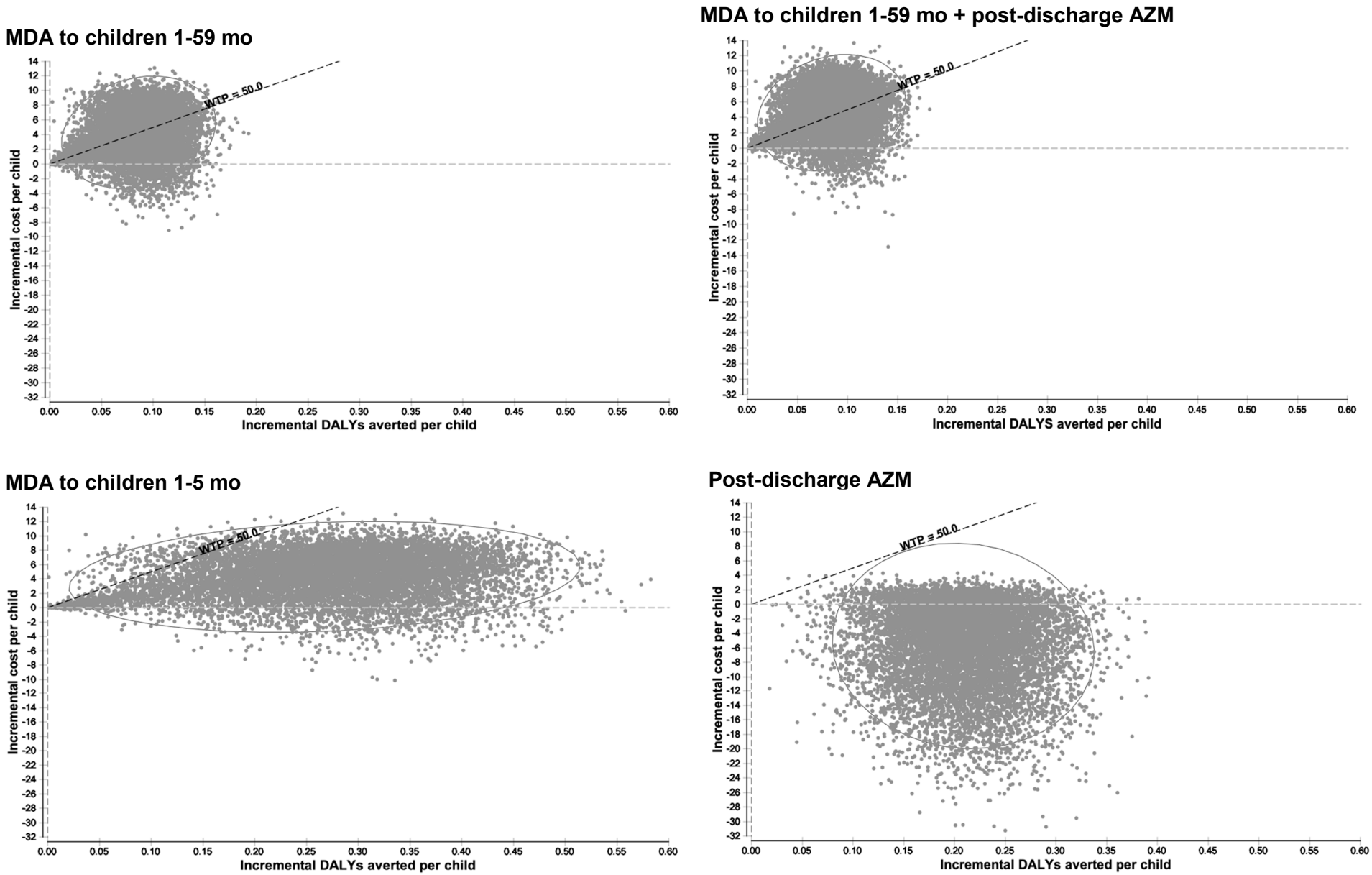


Appendix Figure 1. Visual depiction of the modelling approach to capture effects of AMR (linear decreases in AZM effectiveness and linear increases costs at higher prevalences of AMR)



Appendix Figure 2. Deterministic, two-way sensitivity scenarios in which AZM administration is cost-saving, depending on prevalence of hospitalizations in the target population and the effect of AZM on reducing hospitalization

*Note: all MDA strategies assumed the same hospitalization rates among community-based children



Appendix Figure 3. Scatter plots of results from probabilistic sensitivity analyses

Ellipses represent 95% uncertainty interval, Diagonal lines represent willingness-to-pay threshold ($50/DALY averted)

CONCLUSION

Infectious diseases are the leading cause of childhood deaths in SSA and we evaluated risk factors, interventions, and cost-effectiveness of various strategies for common infectious diseases.

Risks of linear growth faltering following moderate-to-severe diarrhea may be predicted with clinical and sociodemographic characteristics easily collectible at diarrhea presentation. Age, nutritional status at MSD presentation, and severity of disease appear to indicate increased risks of linear growth faltering following diarrhea. Children who were exposed to antibiotics at diarrhea presentation had lower risks of linear growth faltering than those unexposed to antibiotics, after propensity score adjustment for clinical and sociodemographic factors that were associated with antibiotic exposure. The effect was driven by children with a known bacterial pathogen detected which were known to be associated with linear growth faltering, and in those acutely malnourished at diarrhea presentation. Antibiotics may be a useful intervention for protecting against growth faltering in a sub-set of high-risk children but clinical trial evidence and a careful consideration of clinical benefits and negative consequences (such as antibiotic resistance) will be needed for clinical management decisions.

Once an antibiotic is established to be efficacious, cost and cost-effectiveness data are needed for implementation. Micro-costing through medical record abstraction is a useful way to collect detailed data on patient-level costs of hospitalizations for use in cost-effectiveness models. However, this method may result in slightly underestimated costs due to incomplete documentation of resource utilization. Direct observation may lead to more accurate cost data but involves a substantial human resource time requirement and thus is more costly to research budgets. Researchers should select the method that best fits the goals of the project, the research budget and staffing situation, and the importance of the cost parameter in the cost-effectiveness model.

Empiric administration of AZM, a broad-spectrum antibiotic, is likely to be a highly cost-effective intervention for reducing child mortality in SSA. If AZM were to result in even a small reduction in hospitalization rates, the intervention is likely to avert more costs that required to implement, resulting in cost-savings to the payer. Targeting AZM to higher mortality groups, such as children under 6 months of age or children being discharged from hospital, is even more cost-effective and reduces the number of children exposed to antibiotics, which may reduce spread of antibiotic resistance. However, targeted AZM would avert fewer absolute deaths. Further trial evidence of targeted approaches will be needed, and policymakers should consider equity concerns as well as implications for antibiotic resistance when implementing a policy for empiric administration of AZM.

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