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Reduction in diarrheal rates through interventions that prevent unnecessary antibiotic exposure early in life in an observational birth cohort

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Abstract

Background—Antibiotic treatment early in life is often not needed and has been associated with increased rates of subsequent diarrhea. We estimated the impact of realistic interventions, which would prevent unnecessary antibiotic exposures before 6 months of age, on reducing childhood diarrheal rates.

Methods—In data from a prospective observational cohort study conducted in Vellore, India, we used the parametric g-formula to model diarrheal incidence rate differences contrasting the observed incidence of diarrhea to the incidence expected under hypothetical interventions. The interventions prevented unnecessary antibiotic treatments for non-bloody diarrhea, vomiting, and upper respiratory infections before 6 months of age. We also modeled targeted interventions, in which unnecessary antibiotic use was prevented only among children who had already stopped exclusive breastfeeding.

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Author's contributions: HDW and GK conceptualized and designed the study and supervised data collection. RS and DK coordinated data collection and managed the databases. ETR, SBD, and DJW conceptualized the analyses. ETR carried out the analyses and drafted the initial manuscript. All authors critically reviewed the manuscript, and approve the final manuscript as submitted.

Results—More than half of all antibiotic exposures before 6 months (58.9%) were likely unnecessary. The incidence rate difference associated with removing unnecessary antibiotic use before 6 months of age was -0.28 (95% confidence interval: -0.46, -0.08) episodes per 30 child-months. This implies that preventing unnecessary antibiotic exposures in just 4 children would reduce the incidence of diarrhea by one from 6 months to 3 years of age.

Conclusions—Interventions to reduce unnecessary antibiotic use among young children could result in an important reduction in diarrheal rates. This work provides an example application of statistical methods which can further the aim of presenting epidemiologic findings that are relevant to public health practice.

Keywords

diarrhea; antimicrobial use; population intervention effects; public health impact

Background

Antibiotic treatment of childhood illnesses is common around the world, including for uncomplicated cases of acute gastroenteritis (AGE) and upper respiratory infections (URI) [1–3]. However, antibiotic treatment is often unnecessary for these illnesses, which are usually self-limited regardless of etiology [4,5]. Further, antibiotics are not effective against viral pathogens often responsible for these illnesses [1,6,7], and antibiotics may elicit adverse reactions or make the illness worse [1,8]. Indiscriminate antibiotic use also contributes to antimicrobial resistance [1,4,8], which is a critical concern in India where the prevalence of methicillin resistant *Staphylococcus aureus* (MRSA) has been reported at over 40% [9]. Correspondingly, international organizations, including the World Health Organization, recommend against routine use of antibiotics to treat non-bloody diarrhea and URI [1,10,11]. However, inappropriate antibiotic use remains common; several healthcare facility-based studies in India reported antibiotic prescription rates for acute childhood diarrhea as high as 70-90% [12–15].

In a recent publication, we provided evidence that antibiotic treatment of any illness early in life may increase diarrheal risk [16]. Specifically, the relative incidence rate of diarrhea from 6 months to 3 years of age was 33% higher among all children who received at least one course of antibiotics before 6 months of age compared to children who did not receive antibiotics (adjusted incidence rate ratio: 1.33, 95% confidence interval: 1.12, 1.57). There was effect modification by exclusive breastfeeding, such that children who were exclusively breastfed until at least 6 months of age did not have increased diarrheal rates associated with antibiotic exposure [16]. We hypothesize that these effects were mediated by antibiotic-induced alterations of the gastrointestinal microbiota [17], which have been associated with increased intestinal inflammation, intestinal permeability, and susceptibility to infections [18,19].

The effect estimates reported in this previous work compared a counterfactual scenario in which all of the children were exposed to antibiotics to one in which none of the children were exposed to antibiotics. This all-versus-none comparison is the default effect reported in most statistical analyses and is termed the average treatment effect or population average causal effect [20]. This effect implies an intervention that would remove all antibiotic exposures before 6 months of age. However, some illnesses require antibiotic treatment, and the benefits of curing these illnesses likely outweigh any costs associated with future diarrheal risk. Therefore, the population average causal effect represents an intervention that is unrealistic and unethical.

A more plausible public health intervention would be one that prevents only *unnecessary* antibiotic use, such as antibiotic treatment of AGE without bloody stools and URI. Here, we used the parametric g-formula [20–23] to estimate intervention effects that are more relevant to public health policy in addition to the usual exposure effects [20,21,24]. Specifically, we estimated the effects of interventions that would remove only unnecessary antibiotic exposures before 6 months of age, both in the general study population and when targeted to children no longer exclusively breastfed since children who stopped exclusive breastfeeding before 6 months of age had the greatest increase in diarrheal risk associated with antibiotics [16]. These hypothetical public health interventions would be most appropriate in resource poor settings like India where the burden of diarrhea and related morbidity and mortality are greatest.

Methods

We analyzed data from a prospective observational cohort study of immune responses in cryptosporidiosis in 497 children followed from birth to 3 years of age. The study population consisted of all children born in semi-urban slums of Vellore, Tamil Nadu, India between April 2009 and May 2010. The study population, enrollment strategy, and data collection methods have been previously described [25]. Briefly, children of pregnant women were identified and enrolled through consecutive recruitment during repeated household surveys and visits to local antenatal clinics. Children were followed twice-weekly for diarrhea episodes, defined as at least three loose or watery stools in a 24-hour period [10], and antibiotic use. Other illnesses were assessed and treated at a conveniently located and free study clinic. Two-thirds of enrolled families were of low socioeconomic status based on the Kuppuswamy scale [26] and more than half had poor household hygiene [27]. Slightly more than half of children were male (52.9%) and 17.1% were low birth weight (<2.5 kg). The study was approved by the Institutional Review Boards of the Christian Medical College, Vellore, India, Tufts University Health Sciences campus, Boston, & University of North Carolina-Chapel Hill.

The data and analytic definitions have been described in our previous analysis of the effect of early life antibiotic use on diarrheal rates in this study population [16]. Briefly, we used negative binomial regression to estimate incidence rate ratios for diarrhea from 6 months to 3 years comparing children who received any antibiotics before 6 months of age to children who did not. Diarrhea was defined using the standard WHO definition as at least three loose or watery stools in a 24-hour period [10]. Because we did not detect a dose-response relationship between the number of antibiotic courses received and diarrheal rates, we used a binary classification of antibiotic exposure comparing at least one antibiotic course received to no courses received. We adjusted for demographic characteristics and measures of illness in the first 6 months as indicated in the footnote of Table 2.

To classify potentially unnecessary antibiotic use, we characterized antibiotic treatments by indicating diagnosis: AGE (further categorized into bloody diarrhea, non-bloody diarrhea, or vomiting only), URI, and other. Diagnoses for diarrhea and presence of bloody stools were recorded in the cohort study data. Diagnoses for all other illnesses were extracted from study clinic records as documented by clinic physicians. We classified antibiotics for non-bloody diarrhea as “not indicated” according to clinical guidelines. We considered antibiotics for URI and vomiting as “likely not indicated” to reflect the potential variability in clinic diagnosis definitions. Antibiotics given for all other illnesses, including cases of bloody diarrhea, were considered necessary.

Statistical methods

We used the parametric g-formula [20–23,28,29] to estimate intervention contrasts, or comparisons of outcomes between specific index and referent groups, associated with the effect of antibiotic use on diarrheal rates. The procedure for fitting the g-formula was as follows: we 1) estimated beta coefficients for the observed exposure and covariates using the negative binomial model with rates of diarrhea from 6 months to 3 years as the outcome; 2) used the estimated coefficients to predict the incidence rate of diarrhea in all individuals under the index exposure and again under the referent exposure; 3) averaged the predicted outcomes across individuals in the exposure groups; and 4) compared the average outcomes to estimate the population-standardized rate difference. Confidence intervals were constructed by bootstrap of the above steps with 1000 replicates [30]. In implementing the parametric g-formula with negative binomial models, we assume no unmeasured or residual confounding, no selection bias, no measurement error, no model misspecification, independence of outcomes between individuals, and a negative binomial distribution of the diarrhea count outcome [21,22]. We also estimated the number needed to treat (NNT) for each contrast as the reciprocal of the rate difference. In this setting, the “treatment” would be withholding unnecessary antibiotic treatment in the first 6 months of life. Because the NNT is calculated from the rate difference, it is interpreted as the NNT to see a one episode reduction in diarrhea incidence over the 30-month period from 6 months to 3 years of age. The parametric g-formula in this setting is equivalent to parametric standardization to the full population distribution of covariates [28].

We considered two interventions: (i) removing all antibiotics that were classified as not indicated before 6 months of age, and (ii) additionally removing those likely not indicated before 6 months of age. All other antibiotic exposures were not affected by the simulated interventions. Given our binary exposure classification (exposed to at least one course of antibiotics versus none), children remained exposed to antibiotics if they had any necessary antibiotic exposures. Children who received only unnecessary antibiotics moved from exposed to unexposed after the interventions. When targeted, the interventions were applied only to children who were treated after they had stopped exclusive breastfeeding.

The index and referent exposures in the index and comparative groups respectively are described for each contrast in Table 1. The referent exposures correspond to the observed or actual distribution of antibiotic exposure in the observational study in all cases except for the population average causal effect, in which the referent is a counterfactual scenario in which all children were treated with at least one course of antibiotics. The index exposures refer to counterfactual scenarios that would occur if all antibiotic exposures were removed (in the cases of the population average causal effect and population attributable contrast) or if the interventions were to be implemented (in the cases of the generalized and targeted intervention contrasts).

In sensitivity analyses, we estimated the population average and generalized intervention contrasts in the exposed population only. These effects, commonly termed the "effect of treatment in the treated," estimate the contrasts for a target population with the same distribution of covariates as the exposed population instead of as the total study population. Correspondingly, the parametric g-formula in this setting is equivalent to a parametric approach to standardization to the exposed population distribution of covariates [28]. The referent and index exposures are the same as those in the corresponding contrasts in the total study population. These effects are appropriate when effect measure modification is expected by covariates that differ between the exposed and unexposed groups [31–33].

In a second sensitivity analysis, we expanded our models to estimate separate coefficients for the effects of necessary and unnecessary antibiotics and included the interaction between them to account for any differences in the antibiotic effect by indicating condition.

Results

Among 465 children in the parent cohort who remained in the study for more than 6 months (93.6%), 25.4% and 12.6% of antibiotic exposures from birth to 3 years of age were given for non-bloody diarrhea (not indicated) and URI or vomiting (likely not indicated) respectively (Figure 1). Only 30 children (6.5%) received no antibiotics during the 3-year follow-up period. More than half (n=267, 57.4%) of children were given at least one course of antibiotics in the first 6 months of life, among whom the median number of antibiotic courses received was one (mean=1.9, standard deviation=1.14). Nearly one-third of antibiotics before 6 months (32.3%) were not indicated according to our classification, and another 26.6% were likely not indicated. Under Intervention (i), which removed antibiotics that were not indicated (32.3%), 217 children (46.7%) remained exposed to necessary antibiotics. Under Intervention (ii), which removed antibiotics that were not or likely not indicated before 6 months of age (58.9%), only 162 children (34.8%) remained exposed, resulting in more than a 20% absolute reduction in exposed children. The average length of follow-up was 2.29 years (27.24 months).

The effect estimates for each contrast are shown in Table 2. The rate difference associated with the population average causal rate difference was the largest in magnitude (incidence rate difference (IRD): -1.11 diarrhea episodes per 30 person-months, 95% confidence interval (CI): -1.87, -0.36) since this effect represents the most extreme contrast (all children exposed versus none) and does not correspond to a realistic reduction in antibiotic use. The population attributable incidence rate difference (IRD: -0.67 episodes per 30 person-months, 95% CI: -1.13, -0.21) was smaller since the exposure was unchanged among the 42.6% of children who were not exposed to antibiotics before 6 months of age in this index scenario.

We then estimated the contrasts associated with the impact of implementing the hypothetical interventions to reduce antibiotic use. The implementation of Intervention (i) in the total study population—removing antibiotic treatment for non-bloody diarrhea—would result in 0.15 fewer diarrhea episodes per child on average from 6 months to 3 years of age in comparison to the observed diarrheal rates under the observed distribution of antibiotic use in the observational cohort (IRD: -0.15 episodes per 30 person-months, 95% CI: -0.27, -0.03; Table 2). Further removing antibiotics for URI and vomiting in Intervention (ii) would result in nearly double that effect: 0.28 fewer diarrhea episodes per 30 person-months (IRD: -0.28 episodes per 30 person-months, 95% CI: -0.46, -0.08).

The effects of the interventions were smaller in magnitude than the population average causal rate difference since the interventions would remove only a proportion of (rather than all) antibiotic exposures. Comparatively, the generalized intervention rate difference for Intervention (i) was 14% of the population average causal rate difference and 25% of this effect for Intervention (ii), which removed a greater proportion of antibiotics.

The targeted intervention rate differences were smaller in magnitude than the generalized intervention rate differences because while the majority of children stopped exclusive breastfeeding before 6 months (n=394, 84.7%), over half of antibiotic exposures occurred while the children were still exclusively breastfed (55.5%) and were therefore not removed by the targeted intervention (Table 2).

The corresponding NNTs were very low for these effects. Assuming the generalized intervention rate difference for Intervention (ii) was unbiased, we would need to remove unnecessary antibiotic exposures before 6 months of age for only 3.6 children to see a reduction in diarrhea incidence by one episode during the 30 months between 6 months to 3 years of age (NNT: 3.6, 95% CI: 2.2, 12.5; Table 2).

Sensitivity analyses

The population average causal and generalized intervention incidence rate differences among the exposed children were slightly larger in magnitude, though not statistically significantly different, from the corresponding contrasts in the full study population since average rates of diarrhea were higher among the exposed children (4.80 episodes per 30 person-months). For example, the population average causal incidence rate difference in the exposed was -1.17 episodes per 30 person-months (95% CI: -1.96, -0.36). The intervention effects were also larger; the effect of Interventions (i) and (ii) in the exposed were -0.26 (95% CI: -0.47, -0.06) and -0.48 (95% CI: -0.82, -0.13) episodes per 30 person-months respectively. However, similar effects in the exposed and total study population suggest that there were not strong effect measure modifiers of the effect of antibiotics on either the difference or ratio scales. When allowing for different effects of necessary and unnecessary antibiotics in the models, the magnitudes of the estimated contrasts were very similar, though the estimates were less precise (not shown).

Discussion

Estimates of the potential impact of interventions to reduce antibiotic use among children in the first 6 months of life are more relevant to public health policy than our previously reported population average causal effect [20,36,37], which best corresponds to patient-level effects and may be more appropriate when making individual treatment decisions. This effect does not correspond to meaningful or expected changes in diarrheal rates on a population level because some illnesses require antibiotic treatment, and it would be unethical to remove all antibiotic exposures. By estimating the impact of removing only *unnecessary* antibiotics, the generalized intervention incidence rate differences provide a more realistic expectation of the outcomes of public health interventions.

While the estimates of these contrasts are necessarily smaller in magnitude than the population average causal effect since only a portion of antibiotic exposures would be removed, our models suggest that the proposed interventions would have an important impact on child health, as highlighted by the low estimated NNTs (Table 2). Because diarrhea is almost universal and recurring among these children, even a partial reduction of antibiotic exposure could substantially reduce diarrheal rates at the population level. This effect would improve overall child development since diarrhea is a leading cause of death among children in low-resource settings [38] and can lead to life-long morbidity associated with stunted growth and cognitive impairment [39].

We do not calculate NNTs for the population average causal and population attributable incidence rate differences because these effects correspond to unethical interventions, in which even necessary antibiotic exposures would be removed. This would almost certainly lead to negative outcomes associated with severe illnesses being left untreated and could potentially increase risk of death. Investigating such an intervention would be fundamentally uninformative for public health, and we do not have data concerning the complex effects of withholding antibiotic treatment for necessary illnesses that would be required for estimating its impact.

The rate differences for the targeted interventions were smaller than those for the generalized interventions because the targeted interventions prevented antibiotic exposures only after children stopped exclusive breastfeeding. Thus, more children remained exposed under the targeted interventions due to antibiotic use during exclusive breastfeeding. These results suggest that a general intervention applied to all children before 6 months of age would be most effective.

This study was limited by the inability to definitively characterize antibiotic treatment as unnecessary. Only information concerning the indicating illness was available, and other symptoms that may have indicated antibiotic treatment were unknown. A subset of URI and AGE cases could have been of bacterial etiology and responded to antibiotics. In these cases, worse outcomes due to withholding antibiotic treatment might have outweighed effects of increased diarrheal risk. On the other hand, it is also likely that some fever cases were viral and did not require antibiotics, which would make our definition of unnecessary antibiotic use conservative. Our classification is likely reasonable since diagnostic capabilities in the study area are not sufficient to distinguish between bacterial versus viral etiologies, and treatment decisions are informed by international guidelines [1,10,11] and based on clinical signs alone (such as bloody stools during diarrhea). However, in practice, antibiotic treatment decisions should be made on a case-by-case basis and take into account both the potential benefits and harms of antibiotic treatment.

Because there were few severe illnesses and deaths in our cohort, we were unable to estimate the impact of the interventions on more serious diarrhea-related outcomes. We were also unable to model other potential negative outcomes of antibiotic use such as risk of adverse drug reactions, healthcare costs, and development of antimicrobial resistance.

Finally, our use of the g-formula relied on parametric modeling, which like other models, may have been misspecified. However, we expect our model to be appropriate given the model-predicted outcomes matched the observed incidence. The consistency of results in sensitivity analyses further support the assumption of no model misspecification. Because our models did not include a dose-response relationship between diarrheal rates and the number of antibiotic courses received, children who had at least one necessary antibiotic exposure remained exposed under the interventions. Our estimates are therefore likely conservative since they ignore the possibility of a benefit due to reducing, but not eliminating, all antibiotic exposures for a given child.

To understand the impact of early life antibiotics on diarrheal risk, we used the parametric g-formula as a unifying method to estimate multiple exposure and intervention contrasts. The parametric g-formula in the time-fixed setting (in contrast to the time-varying setting) is relatively straightforward to implement, and is a viable alternative to regression modeling that allows simple extensions to estimate population intervention effects in addition to exposure effects [20,23]. The method is also useful for quantitatively comparing interventions, such as universal versus targeted interventions, which have been the subject of much debate [40]. Here, we show that interventions to reduce unnecessary antibiotic use among young children could substantially reduce diarrheal rates. This work responds to recent calls for a consequentialist epidemiology [41] by providing an example application of methods which can further the aim of presenting epidemiologic findings that are relevant to public health practice and implementation science.

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Abbreviations

AGE	acute gastroenteritis

IRD	incidence rate difference
NNT	number needed to treat
URI	upper respiratory infection
CI	confidence interval

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What this Paper Adds

What is already known on this subject

- While some antibiotic treatment in early childhood is required to treat severe illnesses, many antibiotics are given unnecessarily for the treatment of gastrointestinal and respiratory infections.
- Antibiotic exposures can cause long-term changes in the gastrointestinal microbiota and have been shown to affect susceptibility to infections in both animal and human studies.
- Earlier work from this cohort showed that antibiotic treatment early in life was associated with increased rates of diarrhea from 6 months to 3 years of age, especially among children who stopped exclusive breastfeeding before 6 months of age.

What this study adds

- The majority of antibiotic exposures in the first 6 months of life were likely unnecessary.
- Preventing unnecessary antibiotic exposures in 4 children would reduce the incidence of diarrhea by one from 6 months to 3 years of age (NNT: 3.6, 95% CI: 2.2, 12.5).
- Realistic public health interventions that prevent unnecessary antibiotic exposures early in life could substantially reduce diarrheal rates in young children.

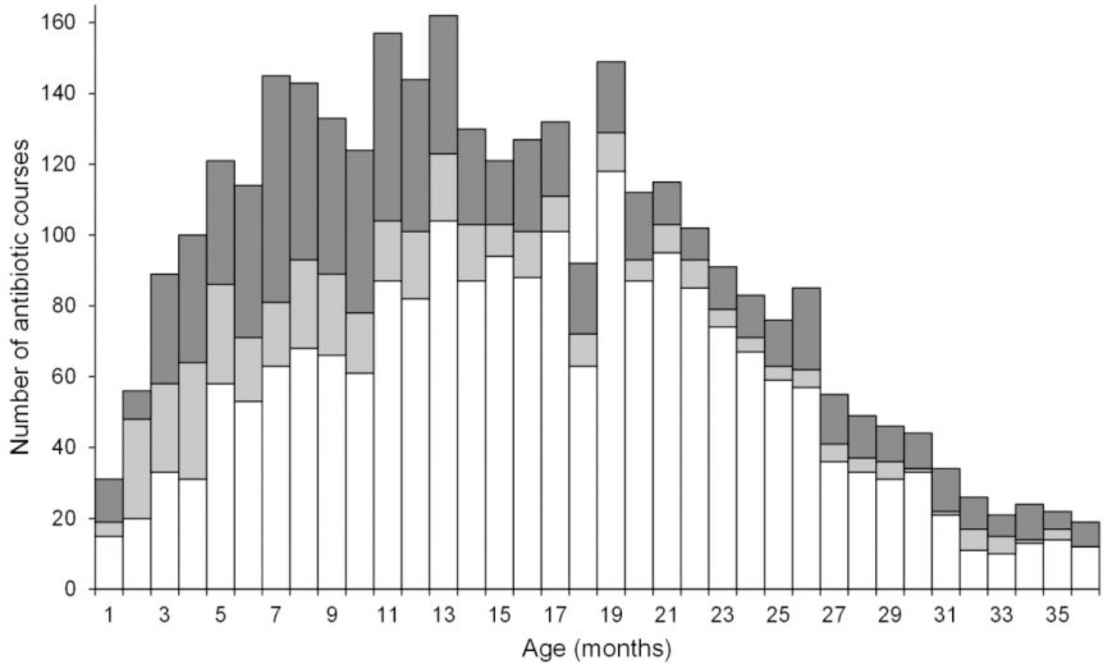

Figure 1.

Number of antibiotic courses received (total n=3,274) by age among 435 children who received at least one course of antibiotics in a birth cohort of 465 children in Vellore, India 2009-2013. Dark gray – antibiotics given for non-bloody diarrhea (not indicated; n=831); light gray – antibiotics given for upper respiratory infections and vomiting (likely not indicated; n=412); white – antibiotics given for other illnesses (n=2,030).

Table 1
Referent and index exposure distributions for effect contrasts

Contrast	Referent exposure	Index exposure
Population average causal effect	The counterfactual exposure distribution had all children been treated with at least one course of antibiotics	The counterfactual exposure distribution had no children been treated with any antibiotics
Population attributable contrast	The observed exposure distribution among all children	The counterfactual exposure distribution had no children been treated with any antibiotics
Generalized intervention contrast	The observed exposure distribution among all children	The counterfactual exposure distributions after each intervention (above, i and ii) among all children
Targeted intervention contrast	The observed exposure distribution among all children	The counterfactual exposure distributions after each intervention (above, i and ii) only among children who were no longer exclusively breastfed at 6 months of age*

*Exposures for children who were exclusively breastfed until at least 6 months did not change from the observed

Table 2

Estimated population-level impact of antibiotic exposure before 6 months of age and of potential interventions to reduce exposure on rates of diarrhea from 6 months to 3 years among 465 children in a birth cohort in Vellore, Tamil Nadu, India 2009-2013

Contrast	Number exposed	Mean rate of diarrhea*	Incidence rate* difference (95% CI)	Number needed to treat§ (95% CI)
Population average causal incidence rate difference				
All exposed	465	4.47	0.	
None exposed	0	3.36	-1.11 (-1.87, -0.36)	
Population attributable incidence rate difference				
Observed	267	4.04	0.	
None exposed	0	3.37	-0.67 (-1.13, -0.21)	
Generalized intervention incidence rate difference				
Observed	267	4.03	0.	
Intervention (i)†	217	3.88	-0.15 (-0.27, -0.03)	6.7 (3.7, 33.3)
Intervention (ii)‡	162	3.75	-0.28 (-0.46, -0.08)	3.6 (2.2, 12.5)
Targeted intervention incidence rate difference				
Observed	267	4.03	0.	
Intervention (i)† in children if no longer exclusively breastfed	237	3.91	-0.12 (-0.20, -0.06)	8.3 (5.0, 16.7)
Intervention (ii)‡ in children if no longer exclusively breastfed	220	3.86	-0.17 (-0.28, -0.08)	5.9 (3.6, 12.5)

*Model estimated rate per 30 person-months from 6 months to 3 years of age, adjusted for exclusive breastfeeding at 6 months of age including an interaction with antibiotic exposure, child sex, socioeconomic status based on the Kuppuswamy scale [26], maternal education, household hygiene [27], household crowding, low birth weight (<2.5 kg), number of diarrhea episodes in first 6 months, total number of days with diarrhea in first 6 months, maximum Vesikari score [34] of diarrhea episodes in first 6 months, number of severe (Vesikari ≥ 11) episodes in first 6 months, prolonged or persistent diarrhea episode in first 6 months, hospitalization for diarrhea in the first 6 months, fever during diarrhea in first 6 months, dehydration during diarrhea in first 6 months, underweight (average weight-for-age z-score before 6 months of age <−2 standard deviations (SD) from the 2006 WHO growth reference [35]), stunting (average height-for-age z-score <−2 SD), and wasting (average weight-for-height z-score <−2 SD) in the first 6 months, any severe illness in first 6 months, number of other infections in first 6 months

†Intervention (i) – removes all antibiotics for the treatment of non-bloody diarrhea (32.3% of antibiotics before 6 months of age)

‡Intervention (ii) – removes all antibiotics for the treatment of non-bloody diarrhea, upper respiratory infection, and vomiting (58.9% of antibiotics before 6 months of age)

§The number of children for whom we would need to prevent unnecessary antibiotic use in the first 6 months of life to expect a one episode reduction in diarrhea incidence over the 30-month period from 6 months to 3 years of age

CI – confidence interval by bootstrap with 1000 resamples