

Reduction in diarrhoeal 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 diarrhoea. We estimated the impact of realistic interventions, which would prevent unnecessary antibiotic exposures before 6 months of age, on reducing childhood diarrhoeal rates.

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

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% CI -0.46 to -0.08) episodes per 30 child-months. This implies that preventing unnecessary antibiotic exposures in just 4 children would reduce the incidence of diarrhoea by 1 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 diarrhoeal rates. This work provides an example application of statistical methods which can further the aim of presenting epidemiological findings that are relevant to public health practice.

BACKGROUND

Antibiotic treatment of childhood illnesses is common around the world, including for uncomplicated cases of acute gastroenteritis (AGE) and upper respiratory infections (URIs).^{1–3} However, antibiotic treatment is often unnecessary for these illnesses, which are usually self-limited regardless of aetiology.^{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* has been

reported at over 40%.⁹ Correspondingly, international organisations, including the WHO, recommend against routine use of antibiotics to treat non-bloody diarrhoea 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 diarrhoea 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 diarrhoeal risk.¹⁶ Specifically, the relative incidence rate of diarrhoea 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 with children who did not receive antibiotics (adjusted incidence rate ratio: 1.33, 95% CI 1.12 to 1.57). There was effect modification by exclusive breast feeding, such that children who were exclusively breast fed until at least 6 months of age did not have increased diarrhoeal rates associated with antibiotic exposure.¹⁶ We hypothesise 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 diarrhoeal 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,



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both in the general study population and when targeted to children no longer exclusively breast fed since children who stopped exclusive breast feeding before 6 months of age had the greatest increase in diarrhoeal risk associated with antibiotics.¹⁶ These hypothetical public health interventions would be most appropriate in resource poor settings like India where the burden of diarrhoea and related morbidity and mortality are greatest.

METHODS

We analysed 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 semiurban slums of Vellore, Tamil Nadu, India between April 2009 and May 2010. The study population, enrolment 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 diarrhoea episodes, defined as at least three loose or watery stools in a 24 h 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 socio-economic status based on the Kuppuswamy scale²⁶ 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; and 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 diarrhoeal rates in this study population.¹⁶ Briefly, we used negative binomial regression to estimate incidence rate ratios for diarrhoea from 6 months to 3 years comparing children who received any antibiotics before 6 months of age to children who did not. Diarrhoea was defined using the standard WHO definition as at least three loose or watery stools in a 24 h period.¹⁰ Because we did not detect a dose–response relationship between the number of antibiotic courses received and diarrhoeal 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 characterised antibiotic treatments by indicating diagnosis: AGE (further categorised into bloody diarrhoea, non-bloody diarrhoea or vomiting only), URI and other. Diagnoses for diarrhoea 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 diarrhoea 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 diarrhoea, 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 diarrhoeal rates. The procedure for fitting the

g-formula was as follows: we (1) estimated β -coefficients for the observed exposure and covariates using the negative binomial model with rates of diarrhoea from 6 months to 3 years as the outcome; (2) used the estimated coefficients to predict the incidence rate of diarrhoea 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-standardised rate difference. CIs 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 diarrhoea 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 diarrhoea 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 standardisation to the full population distribution of covariates.²⁸

We considered two interventions: (1) removing all antibiotics that were classified as not indicated before 6 months of age, and (2) 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 vs 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 breast feeding.

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 generalised and targeted intervention contrasts).

In sensitivity analyses, we estimated the population average and generalised 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 standardisation 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

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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
Generalised intervention contrast	The observed exposure distribution among all children	The counterfactual exposure distributions after each intervention (above, 1 and 2) among all children
Targeted intervention contrast	The observed exposure distribution among all children	The counterfactual exposure distributions after each intervention (above, 1 and 2) only among children who were no longer exclusively breast fed at 6 months of age*

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

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 diarrhoea (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, SD=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 (1), which removed antibiotics that were not indicated (32.3%), 217 children (46.7%) remained exposed to necessary antibiotics. Under intervention (2), 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 diarrhoea episodes per 30 person-months, 95% CI -1.87 to -0.36) since this effect represents the most extreme contrast (all children exposed vs none) and does not correspond to a realistic reduction in antibiotic use. The population attributable IRD (-0.67 episodes per 30 person-months, 95% CI -1.13 to -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 (1) in the total study

Table 2 Estimated population-level impact of antibiotic exposure before 6 months of age and of potential interventions to reduce exposure on rates of diarrhoea 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 diarrhoea*	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 to -0.36)	
Population attributable incidence rate difference				
Observed	267	4.04	0	
None exposed	0	3.37	-0.67 (-1.13 to -0.21)	
Generalised intervention incidence rate difference				
Observed	267	4.03	0	
Intervention (1)‡	217	3.88	-0.15 (-0.27 to -0.03)	6.7 (3.7 to 33.3)
Intervention (2)§	162	3.75	-0.28 (-0.46 to -0.08)	3.6 (2.2 to 12.5)
Targeted intervention incidence rate difference				
Observed	267	4.03	0	
Intervention (1)‡ in children if no longer exclusively breast fed	237	3.91	-0.12 (-0.20 to -0.06)	8.3 (5.0 to 16.7)
Intervention (2)§ in children if no longer exclusively breast fed	220	3.86	-0.17 (-0.28 to -0.08)	5.9 (3.6 to 12.5)

CI by bootstrap with 1000 resamples.

*Model estimated rate per 30 person-months from 6 months to 3 years of age, adjusted for exclusive breast feeding 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 diarrhoea episodes in first 6 months, total number of days with diarrhoea in first 6 months, maximum Vesikari score³⁴ of diarrhoea episodes in first 6 months, number of severe (Vesikari ≥11) episodes in first 6 months, prolonged or persistent diarrhoea episode in first 6 months, hospitalisation for diarrhoea in the first 6 months, fever during diarrhoea in first 6 months, dehydration during diarrhoea in first 6 months, underweight (average weight-for-age z-score before 6 months of age <-2 SDs from the 2006 WHO growth reference³⁵), 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.

†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 diarrhoea incidence over the 30-month period from 6 months to 3 years of age.

‡Intervention (1)—removes all antibiotics for the treatment of non-bloody diarrhoea (32.3% of antibiotics before 6 months of age).

§Intervention (2)—removes all antibiotics for the treatment of non-bloody diarrhoea, upper respiratory infection and vomiting (58.9% of antibiotics before 6 months of age).

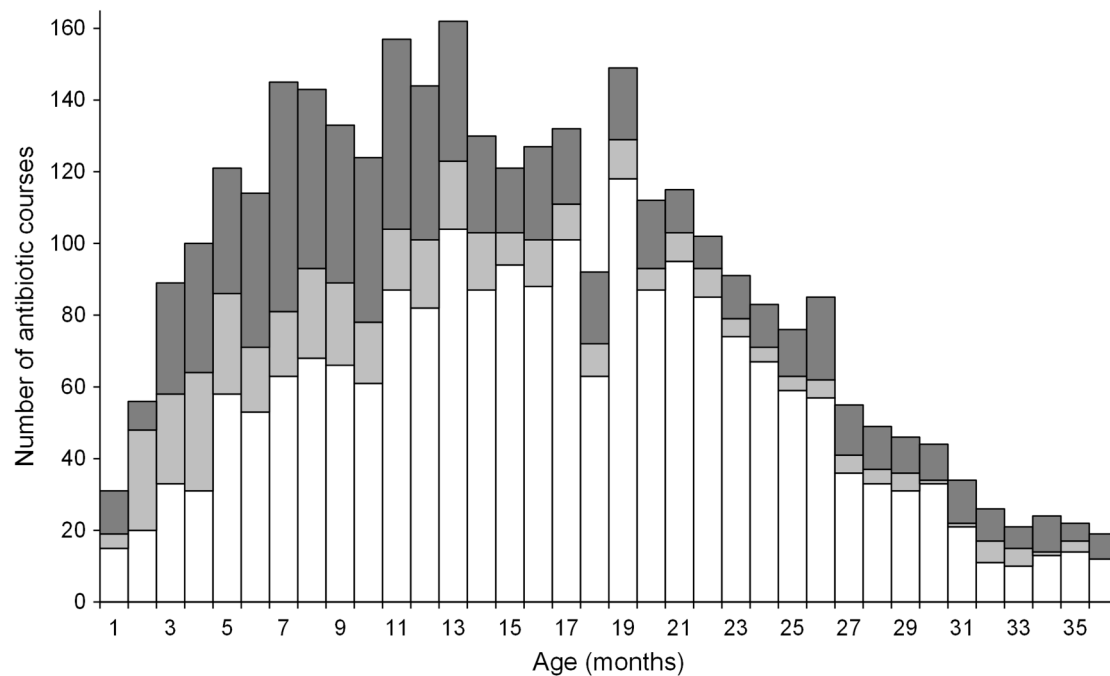


Figure 1 Number of antibiotic courses received (total n=3274) by age among 435 children who received at least one course of antibiotics in a birth cohort of 465 children in Vellore, India, 2009–2013. Dark grey—antibiotics given for non-bloody diarrhoea (not indicated; n=831); light grey—antibiotics given for upper respiratory infections and vomiting (likely not indicated; n=412); white—antibiotics given for other illnesses (n=2030).

population—removing antibiotic treatment for non-bloody diarrhoea—would result in 0.15 fewer diarrhoea episodes per child on average from 6 months to 3 years of age in comparison to the observed diarrhoeal rates under the observed distribution of antibiotic use in the observational cohort (IRD: -0.15 episodes per 30 person-months, 95% CI -0.27 to -0.03 ; table 2). Further removing antibiotics for URI and vomiting in intervention (2) would result in nearly double that effect: 0.28 fewer diarrhoea episodes per 30 person-months (IRD: -0.28 episodes per 30 person-months, 95% CI -0.46 to -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 generalised intervention rate difference for intervention (1) was 14% of the population average causal rate difference and 25% of this effect for intervention (2), which removed a greater proportion of antibiotics.

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

The corresponding NNTs were very low for these effects. Assuming the generalised intervention rate difference for intervention (2) 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 diarrhoea incidence by one episode during the 30 months between 6 months to 3 years of age (NNT: 3.6, 95% CI 2.2 to 12.5; table 2).

Sensitivity analyses

The population average causal and generalised intervention IRDs 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 diarrhoea were higher among the exposed children (4.80 episodes per 30 person-months). For example, the population average causal IRD in the exposed was -1.17 episodes per 30 person-months (95% CI -1.96 to -0.36). The intervention effects were also larger; the effect of interventions (1) and (2) in the exposed were -0.26 (95% CI -0.47 to -0.06) and -0.48 (95% CI -0.82 to -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 diarrhoeal 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 generalised intervention IRDs 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

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estimated NNTs (table 2). Because diarrhoea is almost universal and recurring among these children, even a partial reduction of antibiotic exposure could substantially reduce diarrhoeal rates at the population level. This effect would improve overall child development since diarrhoea is a leading cause of death among children in low resource settings³⁸ 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 IRDs 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 generalised interventions because the targeted interventions prevented antibiotic exposures only after children stopped exclusive breast feeding. Thus, more children remained exposed under the targeted interventions due to antibiotic use during exclusive breast feeding. 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 characterise 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 aetiology and responded to antibiotics. In these cases, worse outcomes due to withholding antibiotic treatment might have outweighed effects of increased diarrhoeal 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 aetiologies, and treatment decisions are informed by international guidelines^{1 10 11} and based on clinical signs alone (such as bloody stools during diarrhoea). 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 diarrhoea-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 modelling, 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 diarrhoeal 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 diarrhoeal 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 modelling 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 diarrhoeal rates. This work responds to recent calls for a consequentialist epidemiology⁴¹ by providing an example application of methods which can further the aim of presenting epidemiological findings that are relevant to public health practice and implementation science.

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 diarrhoea from 6 months to 3 years of age, especially among children who stopped exclusive breast feeding 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 four children would reduce the incidence of diarrhoea by one from 6 months to 3 years of age (number needed to treat: 3.6, 95% CI 2.2 to 12.5).
- ▶ Realistic public health interventions that prevent unnecessary antibiotic exposures early in life could substantially reduce diarrhoeal rates in young children.

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Contributors HDW and GK conceptualised and designed the study and supervised data collection. RS and DK coordinated data collection and managed the databases. ETR, SB-D and DJW conceptualised 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.

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

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