ORIGINAL ARTICLE

Variation in Childhood Diarrheal Morbidity and Mortality in Africa, 2000–2015

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ABSTRACT

BACKGROUND

Diarrheal diseases are the third leading cause of disease and death in children younger than 5 years of age in Africa and were responsible for an estimated 30 million cases of severe diarrhea (95% credible interval, 27 million to 33 million) and 330,000 deaths (95% credible interval, 270,000 to 380,000) in 2015. The development of targeted approaches to address this burden has been hampered by a paucity of comprehensive, fine-scale estimates of diarrhea-related disease and death among and within countries.

METHODS

We produced annual estimates of the prevalence and incidence of diarrhea and diarrhea-related mortality with high geographic detail (5 km^2) across Africa from 2000 through 2015. Estimates were created with the use of Bayesian geostatistical techniques and were calibrated to the results from the Global Burden of Diseases, Injuries, and Risk Factors Study 2016.

RESULTS

The results revealed geographic inequality with regard to diarrhea risk in Africa. Of the estimated 330,000 childhood deaths that were attributable to diarrhea in 2015, more than 50% occurred in 55 of the 782 first-level administrative subdivisions (e.g., states). In 2015, mortality rates among first-level administrative subdivisions in Nigeria differed by up to a factor of 6. The case fatality rates were highly varied at the national level across Africa, with the highest values observed in Benin, Lesotho, Mali, Nigeria, and Sierra Leone.

CONCLUSIONS

Our findings showed concentrated areas of diarrheal disease and diarrhea-related death in countries that had a consistently high burden as well as in countries that had considerable national-level reductions in diarrhea burden. (Funded by the Bill and Melinda Gates Foundation.)

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Diarrhea-related deaths in children are largely preventable. Unfortunately, the burden of diarrhea remains high and inadequately characterized owing to the complex interplay that the environment, food, water, and sanitation have with poverty and deprivation.[1] A considerable proportion of cases of diarrhea can be prevented by rotavirus immunization,[2-4] safe drinking water,[5] safely managed sanitation and hygiene,[6] and the establishment of processes to eliminate exposure to contaminated food.[7] Meanwhile, case management with oral rehydration salts,[8,9] zinc supplementation,[10,11] and antibiotic agents[12] has the potential to prevent persons with diarrhea from dying. Clear information about locations with the greatest diarrheal burden is needed to accelerate progress and to target intervention and treatment programs efficiently.

The Global Burden of Diseases, Injuries, and Risk Factors Study 2016 (GBD 2016) estimated that diarrhea was the third leading cause of death among children younger than 5 years of age in 2015, responsible for an estimated 330,000 deaths (95% credible interval, 270,000 to 380,000) — approximately 2 in 1000 children — and 30 million severe cases (95% credible interval, 27 million to 33 million).[13] Initiatives such as the Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea (GAPPD) establish ambitious goals to address the high burden of diarrhea among children. Precision public health — the use of high-resolution data to guide tailored interventions — is necessary to identify the most vulnerable populations and better target lifesaving preventive and treatment measures.[14]

Previous studies have produced focused analyses of spatial and spatiotemporal variation in diarrheal burden within selected countries.[1,13,15-17] A history of mapping malaria burden,[18,19] mortality rates among children younger than 5 years of age,[20] child-growth failure,[21] and educational attainment[22] has shown the usefulness of household surveys in identifying local patterns of health across the continent and thereby identifying the greatest opportunities for change.

We conducted a systematic assessment of local variation in diarrheal morbidity and mortality among children younger than 5 years of age across Africa during the Millennium Development Goal era (2000–2015). We produced yearly estimates, on a 5-km^2 scale, of the prevalence of diarrhea, the incidence of diarrhea according to disease severity, and diarrhea-related mortality among children younger than 5 years of age from 2000 through 2015 across Africa. These estimates were derived from Bayesian model-based geostatistics (statistics for analyzing spatial and spatiotemporal data), 51,355 geolocated point-level survey clusters, and 2524 small geolocated polygons, in addition to existing methods from the GBD 2016 study.

A Quick Take is available at NEJM.org

METHODS

SURVEY DATA

We compiled a database of 191 surveys from Africa that contained geocoded information corresponding to coordinates of 51,355 survey clusters and 2524 subnational polygon boundaries. Survey clusters are the geographic unit in the sampling design from which households are randomly sampled — often a village, enumeration area, or census tract. For data that we could not match to specific survey clusters (e.g., when global positioning system data were unavailable), we aggregated all the observations to the smallest administrative subdivisions possible for modeling. We aggregated our estimates to first-level administrative subdivisions (e.g., states), second-level administrative subdivisions (e.g., districts), and third-level administrative subdivisions (e.g., municipalities).

We included data from household surveys that measured various health indicators, including the Demographic and Health Surveys, Multiple Indicator Cluster Surveys, and World Bank and country-specific surveys from 1998 through 2016.[23-26] It was more probable that surveys that were not part of a larger series that was conducted independently would be excluded if they did not meet the criteria listed below. All the data collected met the diarrhea case definition of three or more abnormally loose or watery stools within the previous 24 hours in a child younger than 5 years of age. Data were excluded if the source did not record the period prevalence of diarrhea for every child in the home in the preceding 2 to 4 weeks; if the source did not include strata, primary sampling unit, and design weights for each participant; and if the source did not include geographic information that was more specific than at the national scale. Details regarding each data source for each country are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

STATISTICAL ANALYSIS

Prevalence data were adjusted for season and converted from period prevalence to point prevalence as described in the GBD 2016 study.[27] The resulting adjusted point-prevalence data were modeled directly in a Bayesian model–based geostatistical framework, which has been described in detail previously.[1,27] In brief, a spatially and temporally explicit hierarchical logistic-regression model was fit to the point prevalence of diarrhea. In this model, points that are closer together in space and time — and that have similar covariate patterns — are expected to have a similar prevalence of diarrhea. To reflect the social, structural, and environmental factors that may influence the prevalence of diarrhea, we assembled a collection of 27 covariates (Table S3 in the Supplementary Appendix). Posterior distributions of all model parameters and hyperparameters were estimated with the use of R-INLA software (www.r-inla.org).[28,29] Owing to the spatial resolution of the main covariates, all the predictions were made at the 5-km^2 scale. After fitting the geospatial model, we took 1000 samples (hereafter referred to as "draws") from the joint posterior distribution of the prevalence of diarrhea. Each draw contained a single possible diarrheal-prevalence value for each 5-km^2 location for each modeled year.

The GBD 2016 study produced estimates of the prevalence and incidence of diarrhea and diarrhea-related mortality for every country in Africa for each year from 1990 through 2016.[27] We combined our posterior distributions from above with the modeled results and diarrhea-severity distributions from the GBD 2016 study in two stages. First, we maintained consistency with the estimates from the GBD 2016 study by scaling our results such that these 5-km^2 estimates of diarrhea prevalence — when aggregated and averaged to the national level by calculating a population-weighted mean — matched the national-level GBD estimates for each country and year. Second, we converted our calibrated estimates of the point prevalence of diarrhea to our reported measures of incidence and mortality by finding the country-year translation factors that had been estimated as part of the GBD 2016 study at the country-year level. To produce estimates of severe incidence, we multiplied our prevalence estimates by the fraction of diarrhea cases that were categorized by the GBD 2016 study as being severe, divided by the average duration. We produced estimates of mortality by multiplying the estimates of severe incidence by the case fatality rate and then dividing by the severity fraction.

Draws of prevalence, incidence, and mortality were then summarized as mean estimates and Bayesian credible intervals. Aggregated estimates for the administrative subdivisions were also calculated at the draw level and then summarized as population-weighted means with credible intervals. We calculated annual case fatality rates for each country each year by dividing the number of diarrhea-related deaths that had been estimated by the GBD 2016 study by the corresponding number of cases of diarrhea.[30] Model validation was conducted both in sample and out of sample with the use of several hold-out methods. Additional details regarding the model, estimation, and validation processes are provided in Sections 3.0 and 4.0 in the Supplementary Appendix.

This study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendations (Table S1 in the Supplementary Appendix). All the code and data sources that were used for these analyses were available online at http://ghdx.healthdata.org/record/africa-under-5-diarrhea-incidence-prevalence-and-mortality-geospatial-estimates-2000-2015.

RESULTS

DIARRHEA-RELATED MORTALITY

Our findings suggest an unequal distribution of diarrheal burden among children younger than 5 years of age across Africa from 2000 to 2015. Locations in Nigeria and Chad had high mortality rates throughout the study period; these two countries had several first-level administrative subdivisions that exceeded 6 deaths per 1000 children in 2015 (Fig. 1). In 2015, Nigeria had the largest difference observed in the within-country mortality rates, with first-level administrative subdivisions differing by a factor of 6; estimates ranged from 1.6 deaths (95% credible interval, 1.0 to 2.3) per 1000 children in the Bayelsa region to 9.5 deaths (95% credible interval, 7.1 to 12.8) per 1000 children in the Yobe region (Fig. 1).

Our estimates show that the number of deaths due to diarrhea among children younger than 5 years of age in Africa was geographically concentrated. Yobe, Bauchi, and Gombe — the three first-level administrative subdivisions in Ni-

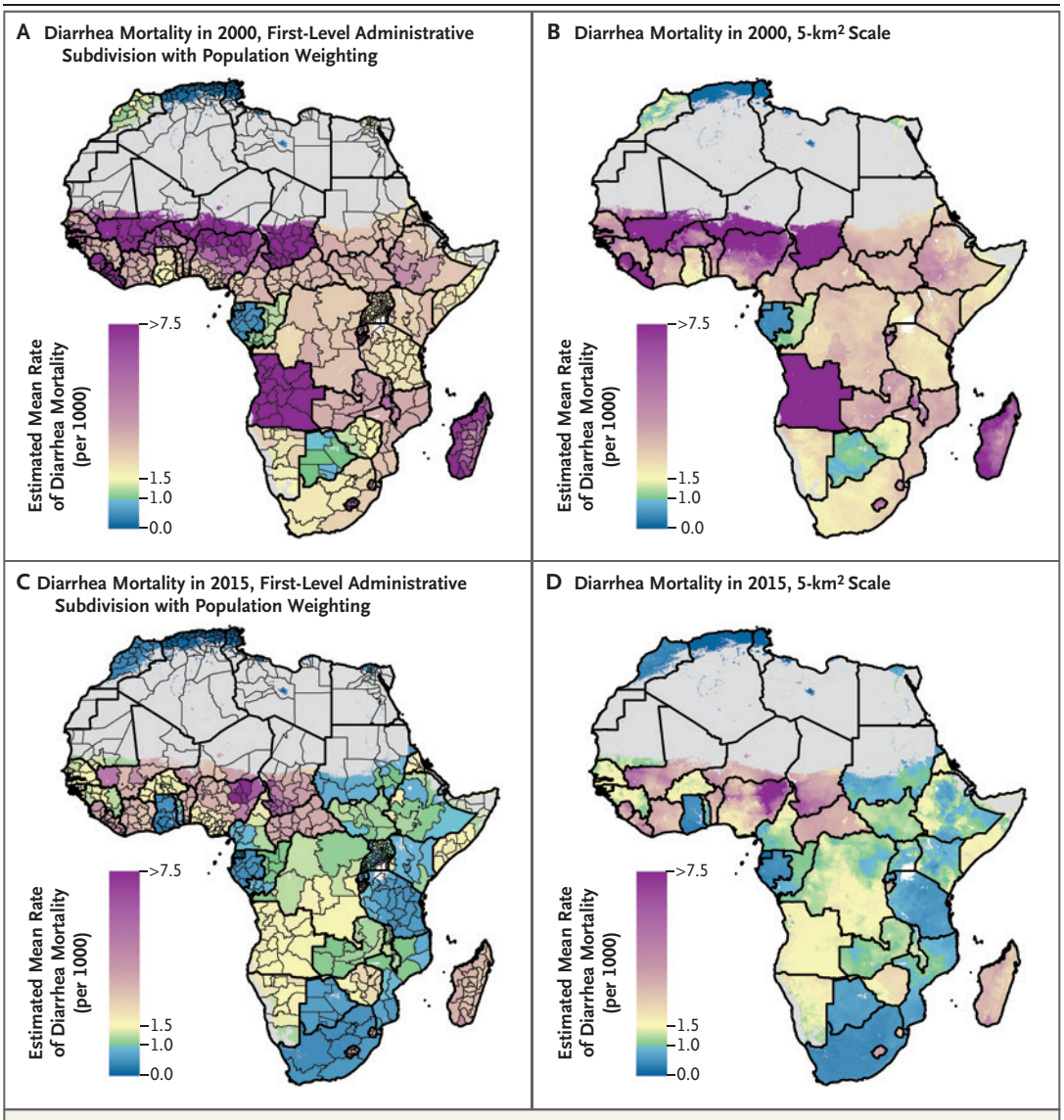

Figure 1. Diarrhea-Related Mortality Rates among Children Younger than 5 Years of Age in 2000 and 2015.

Panels A and B show the estimated mean rate of death attributable to diarrhea per 1000 children in 2000, and Panels C and D the rate in 2015. Panels B and D show the rates for 2000 and 2015, respectively, at the 5-km^2 scale at which the model was fit. Panels A and C show the rates for 2000 and 2015, respectively, aggregated up to first-level administrative subdivision with the use of population weighting. The color scales for mortality are set to indicate the locations in which the mean estimates of the mortality rate met the Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea goal of less than 1 death per 1000 children. Areas with fewer than 10 persons per 1 km^2 or that have been classified as being barren or sparsely vegetated are shown in gray.

geria with the highest mortality rates in Africa — accounted for 6% of all diarrhea-related deaths in Africa while encompassing 1% of the population at risk (with 9900 deaths [95% credible interval, 7600 to 13,000], 4800 deaths [95% credible interval, 3500 to 6500], and 5400 deaths [95% credible interval, 4000 to 7300], respectively) (Fig. 2). More than 50% of all the diarrhea-related deaths among children in Africa were estimated to occur in just 7.0% (55 of 782) of the first-level administrative subdivisions on the continent (encompassing 35% of the population) (Fig. 3).

Although the burden of diarrhea-related deaths varied across the continent, diarrhea-related mor-

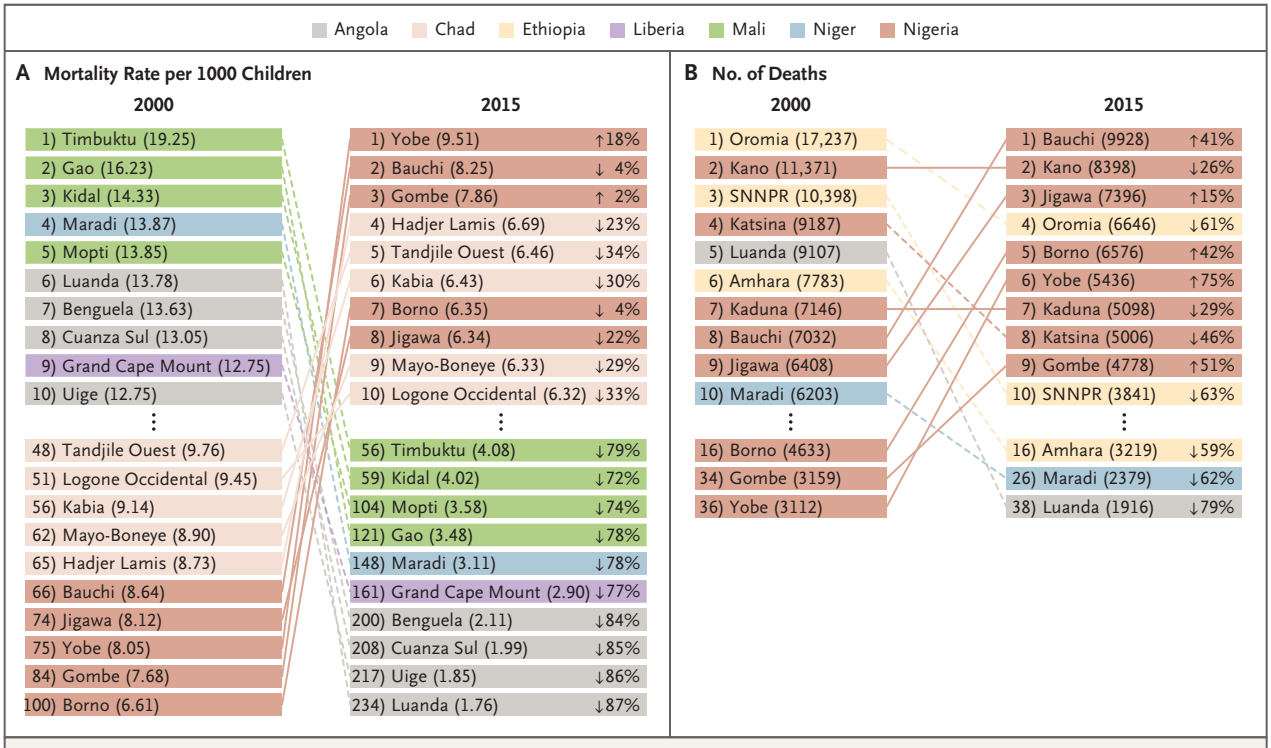

Figure 2. First-Level Administrative Subdivisions with Highest Numbers and Rates of Diarrhea-Associated Death from 2000 to 2015.

Panel A shows the 10 first-level administrative subdivisions with the highest mortality rates (per 1000 children) associated with diarrhea in 2000 and 2015. Panel B shows the 10 first-level administrative subdivisions that had the most childhood death counts associated with diarrhea in 2000 and 2015. Regions that were not in the top 10 in both 2000 and 2015 are listed below vertical ellipses according to the associated year-specific rank. Solid lines connecting the region names indicate that the rank increased or was maintained from 2000 to 2015, and dashed lines indicate that the rank decreased. The relative changes in rate are shown (as percentages) in the two 2015 columns. SNNPR denotes the Southern Nations, Nationalities, and Peoples' Region.

tality rates decreased from 2000 to 2015 in nearly all the locations in Africa. The rates increased in only certain parts of the Central African Republic, Gabon, Ivory Coast, Nigeria, and Zimbabwe (Fig. 1). Given the continental scope and fine spatial scale of this work, additional mortality results are provided in the Supplementary Appendix and are in an online visualization tool (http://vizhub.healthdata.org/lbd/diarrhea).

INCIDENCE OF DIARRHEA

Nigeria contained the regions with the highest rates of cases of severe diarrhea per 1000 children in 2015 (Yobe, Bauchi, and Gombe at 422 cases [95% credible interval, 315 to 569] per 1000 children, 366 cases [95% credible interval, 280 to 480] per 1000, and 349 cases [95% credible interval, 257 to 474] per 1000, respectively) (Fig. 4). The burden of diarrhea incidence was also concentrated in parts of Ethiopia and the Democratic Republic of Congo. In 2015, 9.4% of all the severe cases of diarrhea (2.8 million cases [95% credible interval, 2.39 million to 3.3 million]) in Africa occurred in five first-level administrative subdivisions in these two countries: the Southern Nations, Nationalities, and Peoples' Region (SNNPR), Oromia, and Amhara in Ethiopia and the Orientale and Katanga regions of the Democratic Republic of Congo. Additional incidence results are provided in the Supplementary Appendix and are in an online visualization tool (http://vizhub.healthdata.org/lbd/diarrhea).

CASE FATALITY RATES AND AVERTABLE DEATHS

In 2015, the highest diarrhea-related case fatality rates in Africa were in Lesotho (18 cases per 10,000 children [95% credible interval, 12 to 25]), Mali (17 per 10,000 children [95% credible interval, 12 to 24]), Sierra Leone (16 per 10,000 children [95% credible interval, 11 to 23]), Benin (16 per

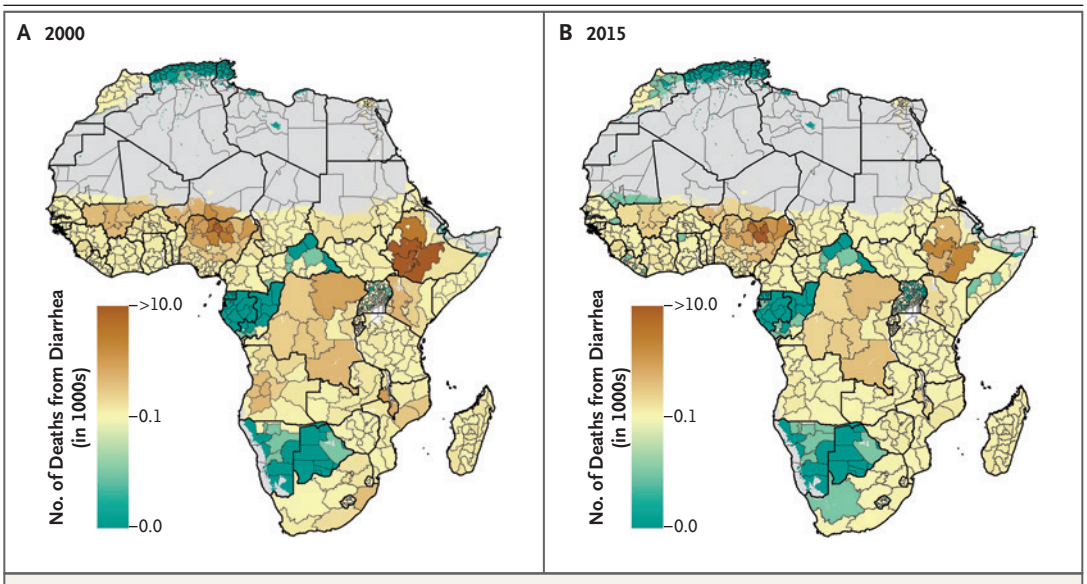

Figure 3. Number of Diarrhea-Related Deaths among Children Younger than 5 Years of Age in 2000 and 2015.
Panel A shows the estimated mean number of diarrhea-related deaths in 2000, and Panel B the number in 2015. Both panels show diarrhea-related death counts aggregated up to the first-level administrative subdivision with the use of population weighting. All the color scales are on a log scale. Areas with fewer than 10 persons per 1 km^2 or that have been classified as being barren or sparsely vegetated are shown in gray.

10,000 children [95% credible interval, 11 to 21]), and Nigeria (16 per 10,000 children [95% credible interval, 11 to 21]) (Fig. 5A). Although the case fatality rate in Benin increased from its estimated value in 2000 (15 cases per 10,000 children [95% credible interval, 10 to 22]), the other four countries listed above had relative decreases from 2000 to 2015.

The median country-level case fatality rate in 2015 was 5 cases per 10,000 children. If all the countries with a case fatality rate greater than the median 2015 value had met that value (scenario 1), an estimated 137,300 deaths (95% credible interval, 119,000 to 158,800) could have been averted across the continent (Fig. 5B). Approximately 53% of these averted deaths (72,400 deaths [95% credible interval, 59,300 to 89,400]) would have occurred in Nigeria. Specifically, Bauchi (6800 deaths averted [95% credible interval, 5200 to 8900]), Kano (5700 deaths averted [95% credible interval, 4200 to 7800]), and Jigawa (5000 deaths averted [95% credible interval, 3700 to 6800]) would have had the most lives saved among the first-level administrative subdivisions in Africa.

The median reduction in the case fatality rate from 2000 to 2015 was 51.4%, which was between that of Cameroon (51.0% [95% credible interval, 26.2 to 70.5]) and that of Kenya (51.8% [95% credible interval, 42.8 to 59.7]). If the countries that had an increase or a reduction in the case fatality rate that was less than the median reduction during this period had reduced their case fatality rate by that median value (scenario 2), approximately 76,000 lives (95% credible interval, 66,200 to 88,000) could have been saved in 2015 (Fig. 5C).

DATA VALIDATION

Validation of model fit and model specification was performed with the use of two instances of fivefold cross validation. Folds were spatially selected with the use of a quad-tree algorithm or according to the second-level administrative subdivision, such that data near each other were selected for the same fold. These strategies test our spatially correlated model by mimicking the spatially patchy nature of our data. Out-of-sample statistics such as the root-mean-square error, correlation, and coverage were generated with the use of data held out of the model and were subsequently summarized by aggregation to administrative areas. Across the continent at the level of the first administrative subdivision, we had a root-mean-square error of 0.01039 in 2000 and

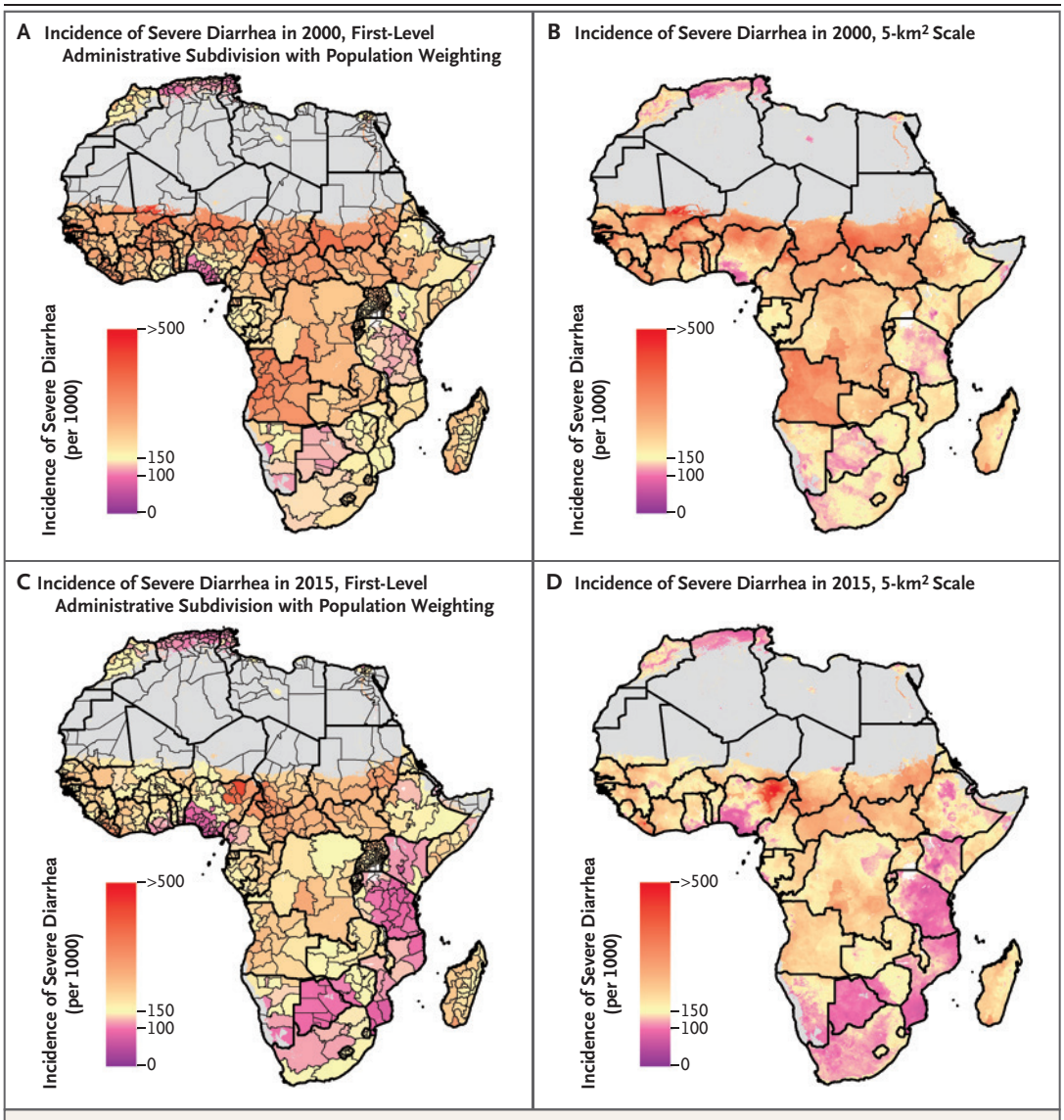

Figure 4. Incidence of Severe Diarrhea among Children Younger than 5 Years of Age in 2000 and 2015.

Panels A and B show the estimated mean rate of severe diarrhea episodes per 1000 children in 2000, and Panels C and D show rates in 2015. Panels A and C show the rates aggregated up to the first-level administrative subdivision with the use of population weighting. Panels B and D show the rates at the 5-km^2 scale at which the model was fit. Areas with fewer than 10 persons per 1 km^2 or that have been classified as being barren or sparsely vegetated are shown in gray.

0.00962 in 2015, whereas the correlations for these years were 0.86 and 0.95, respectively. Estimates of our pixel-level Monte Carlo error varied according to geographic region and year, with values as high as 0.055 in North Africa in 2000 to less than 0.001 in Central Sub-Saharan Africa in 2015. Estimates of our Monte Carlo error according to first-level administrative subdivision were smaller, ranging from 0.025 to 0.0025. Details are shown in Figure S15 in the Supplementary Appendix. Additional statistics regarding model validity are provided in Section 4.0 in the Supplementary Appendix.

DISCUSSION

Our modeled maps show substantial local variation in both the incidence of diarrhea and diar-

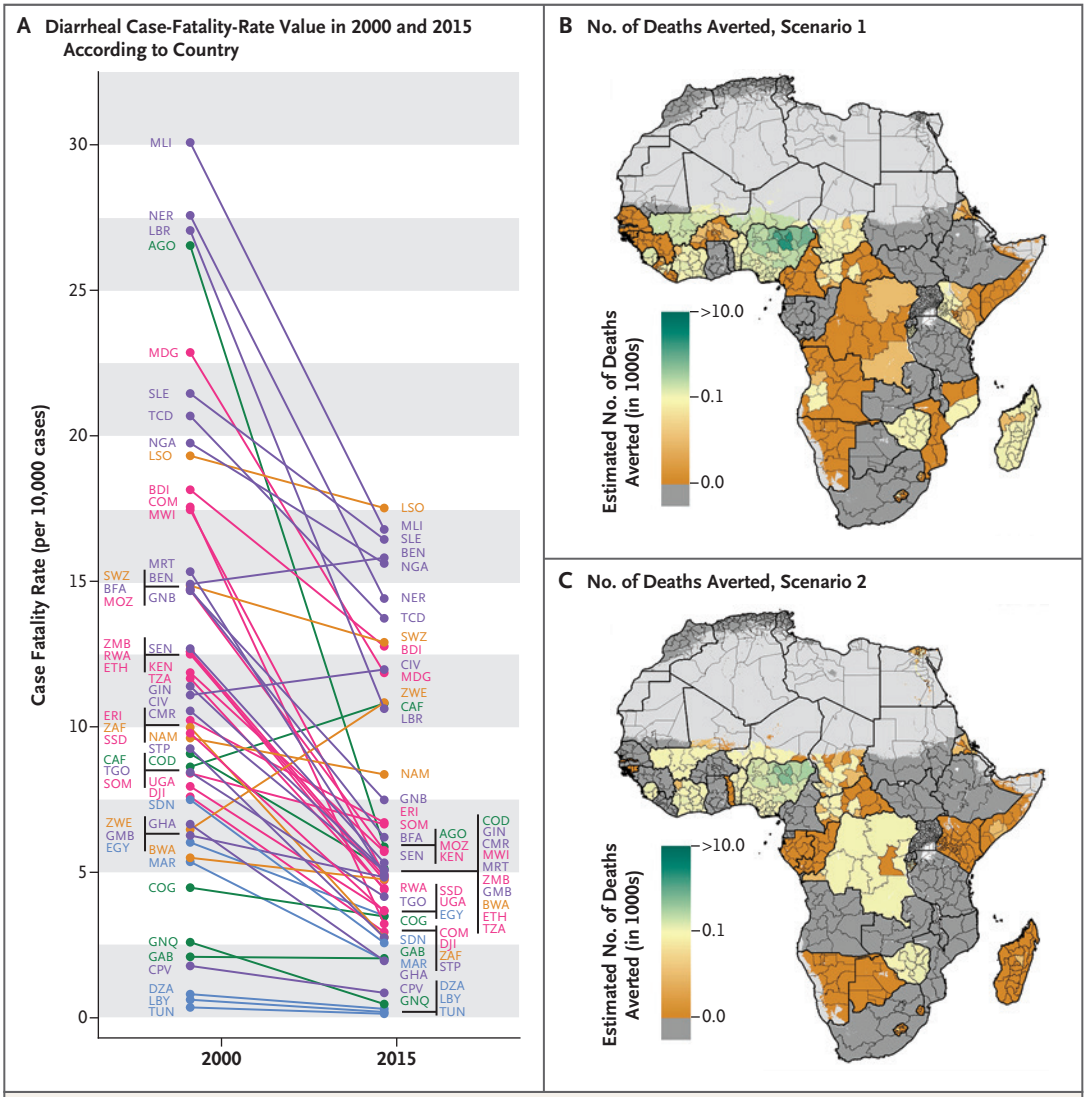

Figure 5. Diarrhea Case Fatality Rate between 2000 and 2015 and Deaths Averted.

Panel A shows the diarrheal case-fatality-rate value of each country in 2000 and in 2015. Colors of the country abbreviations and lines indicate the five regions of Africa: Western Sub-Saharan Africa (purple), Central Sub-Saharan Africa (green), Southern Sub-Saharan Africa (orange), Eastern Sub-Saharan Africa (pink), and North Africa (blue). Panel B shows the estimated number of deaths that would have been averted if all the countries with the highest 50% case fatality rates in 2015 had met the median case fatality rate in 2015 (scenario 1). Panel C shows the estimated number of deaths that would have been averted if the countries with increases or the least decreases in the case fatality rate between 2000 and 2015 had met the median change in rate during that time period (scenario 2). Areas with fewer than 10 persons per 1 km^2 or that have been classified as being barren or sparsely vegetated are shown in gray in Panels B and C. AGO denotes Angola, BDI Burundi, BEN Benin, BFA Burkina Faso, BWA Botswana, CAF Central African Republic, CIV Ivory Coast, CMR Cameroon, COD Democratic Republic of Congo, COG Congo, COM Comoros, CPV Cape Verde, DJI Djibouti, DZA Algeria, EGY Egypt, ERI Eritrea, ETH Ethiopia, GAB Gabon, GHA Ghana, GIN Guinea, GMB Gambia, GNB Guinea-Bissau, GNQ Equatorial Guinea, KEN Kenya, LBR Liberia, LBY Libya, LSO Lesotho, MAR Morocco, MDG Madagascar, MLI Mali, MOZ Mozambique, MRT Mauritania, MWI Malawi, NAM Namibia, NER Niger, NGA Nigeria, RWA Rwanda, SDN Sudan, SEN Senegal, SLE Sierra Leone, SOM Somalia, SSD South Sudan, STP São Tome and Principe, SWZ Swaziland, TCD Chad, TGO Togo, TUN Tunisia, TZA Tanzania, UGA Uganda, ZAF South Africa, ZMB Zambia, and ZWE Zimbabwe.

rhea-related mortality among children younger than 5 years of age in Africa over the period from 2000 to 2015. The rates of decline in incidence and mortality varied both among countries and within countries at every level of spatial aggregation that we considered. Some countries appeared to have substantially reduced their diarrhea burden uniformly, whereas others were behind on their progress countrywide. In addition, the higher-resolution subnational estimates identified a third group of countries in which progress varied subnationally. By providing estimates of current rates and counts of severe incidence and mortality, we identified locations that are most in need of interventions to reduce diarrhea burden.

More than half the diarrhea-related deaths in Africa were estimated to occur in 7% of the first-level administrative subdivisions, which encompass 35% of the population in Africa. These highly populated locations with high mortality rates — many of which are in Nigeria, Ethiopia, and Niger — are places where targeted interventions to reduce mortality, even modestly, could avert many deaths. Conversely, in-depth evaluation of the factors that have contributed to success in countries such as Ethiopia, where the case fatality rate declined by more than 60% from 2000 to 2015, could reveal important strategies for reducing the case fatality rate in other areas. As noted by Troeger and colleagues (on behalf of the GBD Diarrhoeal Diseases Collaborators),[1] Ethiopia has had considerable improvements in child nutrition over the 2000–2015 period. Such improvements, combined with an expanded use of oral rehydration therapy, appears to account for much of the reduction in mortality in that country.[1]

The relative intractability of diarrhea incidence, as compared with diarrhea-related mortality, as shown in the present analysis and elsewhere,[1] may suggest that growing access to timely and appropriate treatment, better nutritional status, and fewer coexisting conditions are contributing factors to reducing diarrhea-related mortality. A variety of interventions — including programs to promote immunization, hygiene, breast-feeding, oral rehydration therapy, and zinc supplementation — have been used effectively on a small scale to combat diarrheal disease and death.[1,31] Targeting the locations with the highest estimated case fatality rates, such as those in Lesotho and Mali, is likely to have a larger effect than untargeted approaches. Although the introduction of the rotavirus vaccine in Africa is relatively recent and coverage is still incomplete, the GBD 2016 study showed that rotavirus vaccine coverage was negatively correlated with all-cause diarrhea. However, the fraction of diarrhea cases attributed to rotavirus varies substantially across Africa (6.5 to 64.2% in 2016). As the vaccine becomes more established, this situation will warrant further investigation.

Local estimates of diarrheal burden can be used to prioritize improved access to safe water and sanitation, which varies greatly between dense and sparse populations[32,33]; childhood-growth monitoring, which has improved in most regions of Africa but not universally[34,35]; delivery and uptake of vaccines, including the rotavirus vaccine[36]; and access to diarrheal care and prevention interventions for marginalized populations that live in remote regions or in areas of conflict.[37,38] Nepal, for example, outpaced its neighboring countries in reducing diarrhea-related case fatality rates in part by implementing a district-level community intervention program.[39] In addition, Brazil successfully used targeted interventions in the 1980s, when it drastically reduced infant mortality due to diarrheal diseases through the use of policy efforts aimed at the northeast of the country, a poorer region that had the highest burden in the country.[40]

As with any work of this scope, our results are subject to several limitations. First, to produce continent-wide estimates, we combined data from a broad range of sources, which required us to make assumptions about their usefulness and consistency. For example, whereas the prevalence of diarrhea was assessed with the use of the same, standard question across health surveys, such surveys rely on respondent-reported stooling patterns and, as such, are subject to recall and reporting bias. Second, there is also evidence of significant differences in risk within the group of children younger than 5 years of age.[41] Owing to the nature of the data and methods we used, we are currently unable to parse mortality and morbidity estimates into finer age groups.[13,42] Third, without an assessment of the interventions used across the continent over time, we are limited in the inferences we can make in this article.

Fourth, conversions from prevalence to incidence leveraged the GBD-modeled estimates and distribution of diarrhea severity. Incorporating cause-specific estimates of the incidence and

severity of diarrhea would probably enhance the accuracy of the conversion and would serve as a valuable tool in the design of appropriate and effective interventions. Similar to the GBD 2016 study, which parsed all-cause diarrhea into percent attributable fractions for multiple causes,[1,27] we are working toward cause-specific maps of mortality and morbidity for Africa. Currently, neither approach uses information about bloody stools to ascertain the severity or cause of the diarrheal episode because that information was not included in all the surveys. Although the conversion from incidence to mortality leverages various data sources[1,13,27] and allows for variation in the case fatality rates according to country, year, sex, and age, it does not currently allow for variation in case fatality rates according to cause of diarrhea and does not incorporate the effects of coexisting conditions.

The data used in our analyses overlapped with but were not identical to the findings of the GBD 2016 study, and although our model had reasonable agreement at the country level with the data we used (Fig. S9 in the Supplementary Appendix), our estimates frequently differed from those of the GBD 2016 study (Fig. S12 in the Supplementary Appendix). We adjusted our estimates to align with those of the GBD 2016 study to maintain consistency with its results and for the purposes of using GBD-level analyses (e.g., case fatality rates) (Section 4.3 in the Supplementary Appendix). Our geospatial approach naturally borrows strength from neighboring areas and, as such, may smooth over extremely focal epidemics, such as those that have frequently been associated with cholera.

This work provides a foundation for several important directions for future research. First, combining these results with hospital-level, clinic-level, and causal agent–specific data may provide increased capacity to create targeted intervention strategies (e.g., coverage needs for the rotavirus vaccine). In the absence of data regarding causal factors, it is difficult to target interventions precisely because some interventions are cause-specific. Second, the exact spatial and temporal information about the implementation of past intervention programs ought to be matched to the corresponding trends in risk in order to look for the signatures of effectiveness. Finally, the approaches outlined in this study are directly applicable to other continents for which similar data sources are available. Expanding the estimates to all low- and middle-income countries will be the next step toward the goal of globally mapping diarrheal morbidity and mortality.

In conclusion, this study showed the marked local variation in childhood morbidity and mortality due to diarrhea across Africa. For every country in Africa, these estimates can be used to identify the regions to target interventions more precisely. Given that the vast majority of diarrheal diseases are attributable to preventable causes of diarrhea,[1] many of these estimated deaths are likely to be preventable at the population and clinical levels.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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REFERENCES

1. GBD Diarrhoeal Diseases Collaborators. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Infect Dis 2017;17:909-48.
2. Parashar UD, Johnson H, Steele AD, Tate JE. Health impact of rotavirus vaccination in developing countries: progress and way forward. Clin Infect Dis 2016;62:Suppl 2:S91-S95.
3. Paternina-Caicedo A, Parashar UD, Alvis-Guzmán N, et al. Effect of rotavirus vaccine on childhood diarrhea mortality in five Latin American countries. Vaccine 2015;33:3923-8.
4. Lamberti LM, Ashraf S, Walker CL, Black RE. A systematic review of the effect of rotavirus vaccination on diarrhea outcomes among children younger than 5 years. Pediatr Infect Dis J 2016;35:992-8.
5. Clasen T, Schmidt W-P, Rabie T, Roberts I, Cairncross S. Interventions to improve water quality for preventing diar-

rhoea: systematic review and meta-analysis. BMJ 2007;334:782.
6. Cairncross S, Hunt C, Boisson S, et al. Water, sanitation and hygiene for the prevention of diarrhoea. Int J Epidemiol 2010;39:Suppl 1:i193-i205.
7. Kirk MD, Angulo FJ, Havelaar AH, Black RE. Diarrhoeal disease in children due to contaminated food. Bull World Health Organ, 2017;95:223034.
8. Munos MK, Walker CLF, Black RE. The effect of oral rehydration solution and recommended home fluids on diarrhoea mortality. Int J Epidemiol 2010;39: Suppl 1:i75-i87.
9. Victora CG, Bryce J, Fontaine O, Monasch R. Reducing deaths from diarrhoea through oral rehydration therapy. Bull World Health Organ 2000;78:1246-55.
10. Walker CLF, Black RE. Zinc for the treatment of diarrhoea: effect on diarrhoea morbidity, mortality and incidence of future episodes. Int J Epidemiol 2010; 39:Suppl 1:i63-i69.
11. Bhutta ZA, Bird SM, Black RE, et al. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. Am J Clin Nutr 2000;72:1516-22.
12. Rogawski ET, Westreich DJ, Becker-Dreps S, et al. Antibiotic treatment of diarrhoea is associated with decreased time to the next diarrhoea episode among young children in Vellore, India. Int J Epidemiol 2015;44:978-87.
13. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1151-210.
14. Dowell SF, Blazes D, Desmond-Hellmann S. Four steps to precision public health. Nature 2016;540:189-91.
15. Azage M, Kumie A, Worku A, Bagtzoglou AC. Childhood diarrhea exhibits spatiotemporal variation in northwest Ethiopia: a SaTScan spatial statistical analysis. PLoS One 2015;10(12):e0144690.
16. Fobil JN, Levers C, Lakes T, Loag W, Kraemer A, May J. Mapping urban malaria and diarrhea mortality in Accra, Ghana: evidence of vulnerabilities and implications for urban health policy. J Urban Health 2012;89:977-91.
17. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459-544.
18. Bhatt S, Weiss DJ, Cameron E, et al. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. Nature 2015;526:207-11.
19. Gething PW, Casey DC, Weiss DJ, et al. Mapping *Plasmodium falciparum* mortality in Africa between 1990 and 2015. N Engl J Med 2016;375:2435-45.
20. Golding N, Burstein R, Longbottom J, et al. Mapping under-5 and neonatal mortality in Africa, 2000-15: a baseline analysis for the Sustainable Development Goals. Lancet 2017;390:2171-82.
21. Osgood-Zimmerman A, Millear AI, Stubbs RW, et al. Mapping child growth failure in Africa between 2000 and 2015. Nature 2018;555:41-7.
22. Graetz N, Friedman J, Osgood-Zimmerman A, et al. Mapping local variation in educational attainment across Africa. Nature 2018;555:48-53.
23. World Bank Group. Core Welfare Indicators Questionnaire survey (CWIQ) (http://ghdx.healthdata.org/series/core-welfare-indicators-questionnaire-survey-cwiq).
24. U.S. Agency for International Development. Demographic and Health Surveys (DHS) (https://dhsprogram.com/).
25. World Bank Group. Living Standards Measurement Survey (LSMS) (http://surveys.worldbank.org/lsms).
26. UNICEF. Multiple Indicators Cluster Surveys (MICS) (http://mics.unicef.org/).
27. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1211-59.
28. Rue H, Martino S, Chopin N. Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations. J R Stat Soc [B] Stat Methodol 2009;71:319-92.
29. Martins TG, Simpson D, Lindgren F, Rue H. Bayesian computing with INLA: new features. Comput Stat Data Anal 2013;67:68-83.
30. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1603-58.
31. Hill Z, Kirkwood B, Edmond K. Family and community practices that promote child survival, growth and development: a review of the evidence. Geneva: World Health Organization, 2004 (http://apps.who.int/iris/bitstream/10665/42924/1/9241591501.pdf).
32. Soares LCR, Griesinger MO, Dachs JNW, Bittner MA, Tavares S. Inequities in access to and use of drinking water services in Latin America and the Caribbean. Rev Panam Salud Publica 2002;11:386-96.
33. Wolf J, Bonjour S, Prüss-Ustün A. An exploration of multilevel modeling for estimating access to drinking-water and sanitation. J Water Health 2013;11:64-77.
34. Onyango AW. Promoting healthy growth and preventing childhood stunting: a global challenge. Matern Child Nutr 2013;9:Suppl 2:1-5.
35. de Onis M, Blössner M, Borghi E. Prevalence and trends of stunting among pre-school children, 1990-2020. Public Health Nutr 2012;15:142-8.
36. Mvula H, Heinsbroek E, Chihana M, et al. Predictors of uptake and timeliness of newly introduced pneumococcal and rotavirus vaccines, and of measles vaccine in rural Malawi: a population cohort study. PLoS One 2016;11(5):e0154997.
37. Bulled N, Singer M, Dillingham R. The syndemics of childhood diarrhoea: a biosocial perspective on efforts to combat global inequities in diarrhoea-related morbidity and mortality. Glob Public Health 2014;9:841-53.
38. Degomme O, Guha-Sapir D. Patterns of mortality rates in Darfur conflict. Lancet 2010;375:294-300.
39. Ghimire M, Pradhan YV, Maskey MK. Community-based interventions for diarrhoeal diseases and acute respiratory infections in Nepal. Bull World Health Organ 2010;88:216-21.
40. Victora CG, Olinto MT, Barros FC, Nobre LC. Falling diarrhoea mortality in northeastern Brazil: did ORT play a role? Health Policy Plan 1996;11:132-41.
41. Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. Lancet 2013; 382:209-22.
42. Liu J, Platts-Mills JA, Juma J, et al. Use of quantitative molecular diagnostic methods to identify causes of diarrhoea in children: a reanalysis of the GEMS case-control study. Lancet 2016;388:1291-301.