

# Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000–2013

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**Background.** Rotavirus vaccine is recommended for routine use in all countries globally. To facilitate decision making on rotavirus vaccine adoption by countries, help donors prioritize investments in health interventions, and monitor vaccine impact, we estimated rotavirus mortality for children <5 years of age from 2000 to 2013.

**Methods.** We searched PubMed using the keyword “rotavirus” to identify studies that met each of the following criteria: data collection midpoint in year 1998 or later, study period of a 12-month increment, and detection of rotavirus infection by enzyme immunoassay in at least 100 children <5 years of age who were hospitalized with diarrhea and systematically enrolled through active surveillance. We also included data from countries that participated in the World Health Organization (WHO)–coordinated rotavirus surveillance network between 2008 and 2013 that met these criteria. To predict the proportion of diarrhea due to rotavirus, we constructed a multiple linear regression model. To determine the number of rotavirus deaths in children <5 years of age from 2000 to 2013, we multiplied annual, country-specific estimates of the proportion of diarrhea due to rotavirus from the regression model by the annual number of WHO-estimated child deaths caused by diarrhea in each country.

**Results.** Globally, we estimated that the number of rotavirus deaths in children <5 years of age declined from 528 000 (range, 465 000–591 000) in 2000 to 215 000 (range, 197 000–233 000) in 2013. The predicted annual rotavirus detection rate from these studies declined slightly over time from 42.5% (95% confidence interval [CI], 37.4%–47.5%) in 2000 to 37.3% (95% CI, 34.2%–40.5%) in 2013 globally. In 2013, an estimated 47 100 rotavirus deaths occurred in India, 22% of all rotavirus deaths that occurred globally. Four countries (India, Nigeria, Pakistan, and Democratic Republic of Congo) accounted for approximately half (49%) of all estimated rotavirus deaths in 2013.

**Discussion.** While rotavirus vaccine had been introduced in >60 countries worldwide by the end of 2013, the majority of countries using rotavirus vaccine during the review period were low-mortality countries and the impact of rotavirus vaccine on global estimates of rotavirus mortality has been limited. Continued monitoring of rotavirus mortality rates and deaths through rotavirus surveillance will aid in monitoring the impact of vaccination.

**Keywords.** rotavirus; diarrhea; child mortality.

Rotavirus is the most common cause of severe diarrhea among children <5 years of age globally. Since 2006, 2 rotavirus vaccines (RotaTeq, Merck & Co and Rotarix, GSK Biologicals) have been licensed in >100 countries worldwide [1, 2]. In 2009, the World Health Organization (WHO) recommended that all countries, and particularly those countries with high diarrhea mortality rates in children, introduce rotavirus vaccines into their national immunization programs [3]. By the end of 2014, >70 countries had introduced rotavirus vaccine into their routine immunization programs for children.

Several countries that have implemented routine childhood vaccination against rotavirus have documented a tremendous impact on severe diarrhea and rotavirus disease requiring

hospitalization [4]. Additionally, some countries, including Mexico, Brazil, and Panama, have documented substantial decreases of 22%–50% in diarrhea mortality among children <5 years of age following vaccine introduction [5–8]. However, rotavirus vaccine implementation in settings of high child mortality in Africa and Asia is just beginning to occur, and the real life-saving potential of vaccination has yet to be realized. To facilitate decision making on rotavirus vaccine adoption by countries and to help donors prioritize investments in health interventions, up-to-date estimates of childhood mortality from rotavirus are needed. Furthermore, baseline estimates of rotavirus mortality are required to measure the impact of vaccination.

The latest WHO estimate of 453 000 rotavirus deaths in children globally was derived using data on overall childhood mortality from diarrhea in the year 2008 and applying the then-available surveillance data on rotavirus detection rates in children hospitalized with diarrhea [9]. Availability of new data and the use of new methods have resulted in several updated estimates of diarrhea mortality among children in recent years [10–13]. In 2010, diarrhea mortality was estimated at 1.24 million deaths among

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children <5 years of age in 2008. In 2013, this estimate was updated to 752 000 diarrheal deaths among children <5 years of age in 2008, a 39% decline from the previous 2008 estimate in 2010 [14, 15]. Additionally, the WHO's Global Network for Rotavirus Surveillance has expanded since its inception in 2008 and includes data from many countries where rotavirus burden data were not previously available [16, 17].

Our objective was to derive updated estimates of rotavirus mortality for children <5 years of age for the period 2000–2013 using updated estimates of diarrhea mortality, hospital-based studies, and surveillance data on rotavirus disease burden, and incorporating the impact of rotavirus vaccine use in early adopting countries.

## METHODS

### Search Strategy and Selection Criteria

To determine the proportion of diarrhea deaths attributable to rotavirus, we used the same literature search and selection criteria as those used for previous WHO rotavirus mortality estimates [9, 18]. We searched PubMed using the keyword “rotavirus” as the primary search term to identify rotavirus surveillance studies published from January 1998 through December 2014 that met our inclusion criteria. To be included in the analysis, a study had to meet each of the following criteria: a data collection midpoint in the year 1998 or later, study period of a 12-month increment (to account for possible seasonality in rotavirus disease), and detection of rotavirus infection by enzyme immunoassay (EIA) in at least 100 children <5 years of age who were hospitalized with diarrhea and systematically enrolled through active surveillance. We also included data from countries that participated in the WHO-coordinated rotavirus surveillance network between 2008 and 2013 that met the above-mentioned criteria [17, 16]. For studies that included data from several countries and/or several sites within a country, we entered each country and site into our database as separate data points, where possible. Similarly, for sites that had multiple years of surveillance data, we separately entered the data from each year into our database, when possible. Eligible studies were identified and the data abstracted by a single author (J. E. T.) and reviewed by a second author (U. D. P.). For each study that satisfied our inclusion criteria, we abstracted the start and end dates of the study period, the country in which the study was conducted, the number of fecal specimens tested, the number of rotavirus-positive results, and the proportion of positive results.

### Data Analysis

To predict the proportion of diarrhea deaths due to rotavirus, we constructed a multiple linear regression model with the midpoint of the study period, the under-5 child mortality estimate during the midpoint of the study period for the country where the study was conducted, the region where the country is located, and an indicator as to whether the study was conducted

before or after rotavirus vaccine introduction into the country's national immunization program as the independent variables. The country-/year-specific under-5 mortality estimates were from the United Nations (UN) Inter-agency Group for Child Mortality Estimation [19]. Countries were classified into regions using the current UN Millennium Development Goals regional groupings [19]. A study was considered as conducted during the post-vaccine introduction period if the midpoint of the data collection period was at least 1 full year after the year of national vaccine introduction and vaccine coverage among children <1 year of age was  $\geq 60\%$ . For example, if a country introduced rotavirus vaccine in 2008, it would be classified as post-vaccine introduction starting in 2010 if vaccine coverage was  $\geq 60\%$  and pre-vaccine introduction otherwise. Vaccine coverage estimates were obtained from the 2013 WHO/United Nations Children's Fund national immunization coverage data [20].

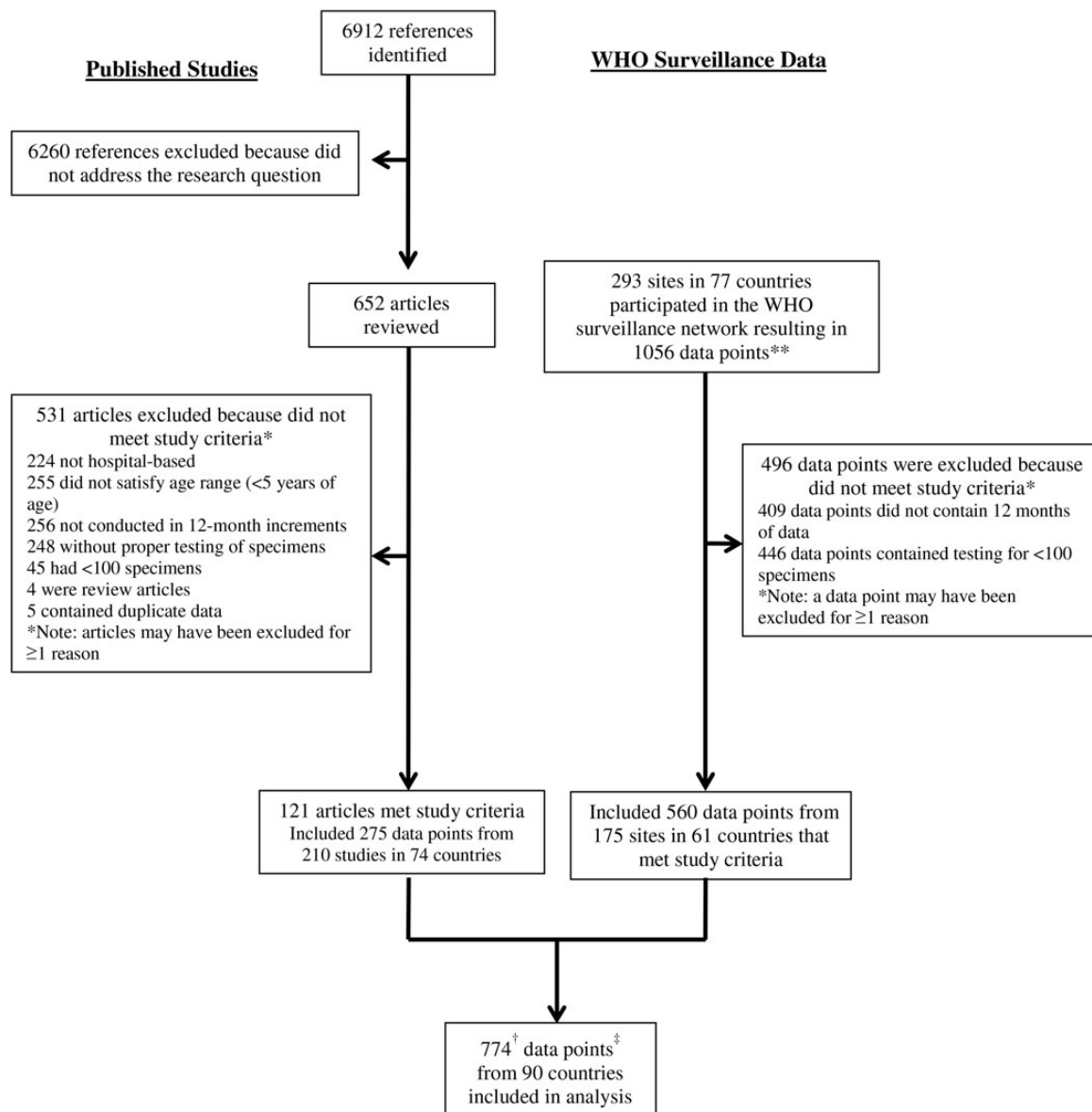
To determine the number of deaths due to rotavirus in children <5 years of age from 2000 to 2013, we multiplied annual, country-specific estimates of the proportion of diarrhea due to rotavirus by the annual number of WHO-estimated child deaths caused by diarrhea in each country [15]. We then summed up these estimates to obtain the annual regional and global estimates of the number of deaths due to rotavirus in children <5 years of age. To calculate annual rotavirus-specific mortality rates per 100 000 children <5 years of age from 2000 to 2013, we used as denominator the 2012 revision of the UN Population Division estimates for the population aged <5 years [21].

## RESULTS

### Trends in Rotavirus Mortality From 2000 to 2013

Specimens from 448 139 children <5 years of age hospitalized for diarrhea were tested for rotavirus by EIA from surveillance studies in 90 countries that met our inclusion criteria, including 269 968 specimens from 121 published articles from 74 countries and 229 527 specimens from 175 WHO-supported surveillance sites in 61 countries (Figure 1). The predicted annual rotavirus detection rate from these studies declined slightly over time from 42.5% (95% confidence interval [CI], 37.4%–47.5%) in 2000 to 37.3% (95% CI, 34.2%–40.5%) in 2013 globally (Table 1). The rotavirus detection rate also declined slightly over the study period in all of the regions except Latin America, where the detection rate began to decline more sharply in 2008, and Northern Africa and developed countries, where the detection rates began to decline more sharply in 2012 (Figure 2B). The highest predicted rotavirus detection rates were in Southeast Asia (50.7%–54.6%) and the lowest rates were in Latin America (26.1%–35.5%).

Globally, we estimated that the number of rotavirus deaths in children <5 years of age declined from 528 000 (range, 465 000–591 000) in 2000 to 215 000 (range, 197 000–233 000) in 2013 (Figure 2A). The largest number of rotavirus deaths occurred in sub-Saharan Africa, where the number ranged from 250 000 (range, 217 000–282 000) deaths in 2000 to 121 000



**Figure 1.** Flowchart of articles and studies included in the analysis. \*\*A data point is the smallest subunit of data that meets all inclusion criteria. For the World Health Organization (WHO) surveillance data, calendar years were used to define 12-month surveillance periods. For example, a site that continuously enrolled patients and tested at least 100 specimens per year from June 2008 to December 2013 would contribute 6 data points, 5 of which (calendar years 2009–2013) would be included in the analysis. †Duplicate data points (ie, published surveillance data) were excluded. ‡Data points may include data from >1 site.

(range, 111 000–131 000) deaths in 2013. Rotavirus deaths decreased at a slower rate in sub-Saharan Africa than in the other regions, resulting in an increasing proportion of all rotavirus deaths occurring in this region from 47.3% in 2000 to 56.3% in 2013. More than 90% of rotavirus deaths occurred in countries eligible for Gavi support [22]. From 2000 to 2013, the largest number of rotavirus deaths occurred in India.

#### Country and Regional Distribution of Deaths in 2013

In 2013, an estimated 47 100 rotavirus deaths occurred in India, 22% of all deaths due to rotavirus that occurred globally

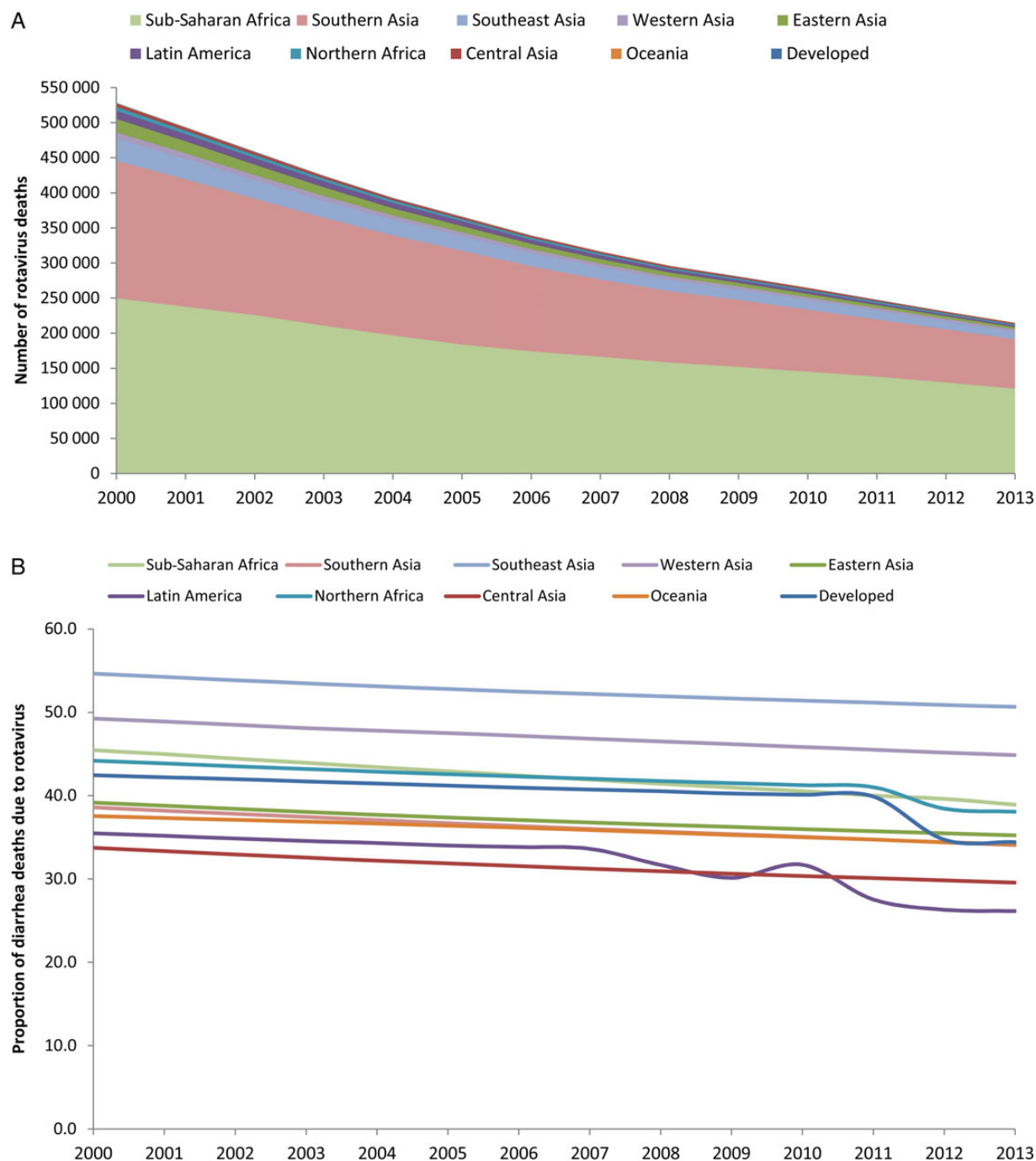
that year. Four countries (India, Nigeria, Pakistan, and Democratic Republic of Congo) accounted for approximately half (49%) of all rotavirus deaths in 2013, and 10 countries (India, Nigeria, Pakistan, Democratic Republic of Congo, Angola, Ethiopia, Afghanistan, Chad, Niger, and Kenya) accounted for almost two-thirds of all deaths (65%) in 2013 (Figures 3 and 4A). In 2013, the highest rate of rotavirus mortality occurred in Angola (240 per 100 000 children <5 years of age). By 2013, all 10 of the countries with a mortality rate >100 per 100 000 children were located in sub-Saharan Africa (Figure 4B).

**Table 1. Estimated Number of Diarrhea Deaths, Rotavirus Deaths, and the Proportion of Death Due to Rotavirus by Region, 2000–2013**

Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
<b>Developed countries</b>														
Diarrhea deaths	2127	1932	1776	1616	1487	1363	1278	1192	1182	1210	1206	1164	1019	977
RV deaths	903	815	741	674	616	562	523	486	479	487	484	464	354	336
% RV <sup>+</sup>	42.5	42.2	42.0	41.7	41.5	41.2	41.0	40.7	40.5	40.3	40.1	39.9	34.7	34.4
<b>Latin America</b>														
Diarrhea deaths	32 780	29 509	27 360	24 922	21 981	20 636	17 767	15 558	13 745	12 338	12 308	9977	9057	8750
RV deaths	11 631	10 382	9536	8612	7543	7021	6011	5231	4355	3718	3903	2747	2383	2288
% RV <sup>+</sup>	35.5	35.2	34.9	34.6	34.3	34.0	33.8	33.6	31.7	30.1	31.7	27.5	26.3	26.1
<b>Central Asia</b>														
Diarrhea deaths	12 172	10 849	9814	8942	8289	7729	7288	6908	6654	6699	6352	5947	5532	5088
RV deaths	4106	3616	3233	2912	2670	2463	2299	2158	2058	2053	1929	1790	1650	1504
% RV <sup>+</sup>	33.7	33.3	32.9	32.6	32.2	31.9	31.5	31.2	30.9	30.6	30.4	30.1	29.8	29.6
<b>Eastern Asia</b>														
Diarrhea deaths	48 713	43 841	38 153	32 420	27 528	23 494	20 583	17 970	15 879	14 368	12 858	11 596	10 482	9776
RV deaths	19 077	17 004	14 656	12 336	10 379	8780	7629	6609	5797	5208	4627	4144	3719	3445
% RV <sup>+</sup>	39.2	38.8	38.4	38.1	37.7	37.4	37.1	36.8	36.5	36.2	36.0	35.7	35.5	35.2
<b>Southeast Asia</b>														
Diarrhea deaths	59 052	53 795	49 266	45 086	41 824	38 796	36 176	34 050	31 468	29 092	27 100	24 947	22 732	21 252
RV deaths	32 263	29 183	26 531	24 112	22 214	20 481	18 980	17 771	16 338	15 027	13 931	12 760	11 567	10 765
% RV <sup>+</sup>	54.6	54.2	53.9	53.5	53.1	52.8	52.5	52.2	51.9	51.7	51.4	51.2	50.9	50.7
<b>Southern Asia</b>														
Diarrhea deaths	507 488	475 557	438 586	410 180	384 734	363 901	332 892	305 137	284 937	269 330	252 515	235 368	219 919	205 858
RV deaths	195 807	181 661	165 884	153 585	142 606	133 529	120 985	109 894	101 679	95 314	88 547	81 748	75 641	70 109
% RV <sup>+</sup>	38.6	38.2	37.8	37.4	37.1	36.7	36.3	36.0	35.7	35.4	35.1	34.7	34.4	34.1
<b>Western Asia</b>														
Diarrhea deaths	17 394	15 947	15 011	14 246	12 822	12 147	11 410	10 320	9592	8830	8105	7570	7376	7006
RV deaths	8566	7796	7278	6852	6130	5770	5383	4833	4460	4077	3715	3446	3331	3143
% RV <sup>+</sup>	49.2	48.9	48.5	48.1	47.8	47.5	47.2	45.8	46.5	46.2	45.8	45.5	45.2	44.9
<b>Oceania</b>														
Diarrhea deaths	1582	1596	1652	1561	1375	1519	1457	1462	1447	1308	1403	1391	1297	1212
RV deaths	594	596	613	576	504	553	526	524	515	462	491	483	446	414
% RV <sup>+</sup>	37.5	37.3	37.1	36.9	36.6	36.4	36.1	35.9	35.6	35.3	35.0	34.7	34.4	34.2
<b>Northern Africa</b>														
Diarrhea deaths	12 276	10 952	10 053	8924	8044	7235	6532	6199	5993	5654	5364	5208	5091	4708
RV deaths	5426	4804	4375	3855	3449	3081	2763	2605	2502	2346	2213	2136	1957	1792
% RV <sup>+</sup>	44.2	43.9	43.5	43.2	42.9	42.6	42.3	42.0	41.8	41.5	41.3	41.0	38.4	38.1
<b>Sub-Saharan Africa</b>														
Diarrhea deaths	549 092	528 612	507 750	479 848	453 237	428 660	410 557	397 038	381 474	371 016	357 680	344 667	327 711	310 967
RV deaths	249 612	237 746	225 705	210 837	196 757	183 953	174 133	166 477	158 084	152 045	145 022	137 913	129 794	121 009
% RV <sup>+</sup>	45.5	45.0	44.5	43.9	43.4	42.9	42.4	41.9	41.4	41.0	40.5	40.0	39.6	38.9
<b>Total</b>														
Diarrhea deaths	1 242 675	1 172 590	1 099 410	1 027 745	961 321	905 480	845 931	795 832	752 371	719 847	684 891	647 835	610 215	575 594
RV deaths	527 984	493 603	458 550	424 350	392 868	366 193	339 232	316 587	296 266	280 737	264 862	247 632	230 843	214 806
% RV <sup>+</sup>	42.5	42.1	41.7	41.3	40.9	40.4	40.1	39.8	39.4	39.0	38.7	38.2	37.8	37.3

Data are presented as No. unless otherwise specified.

Abbreviation: RV, rotavirus.

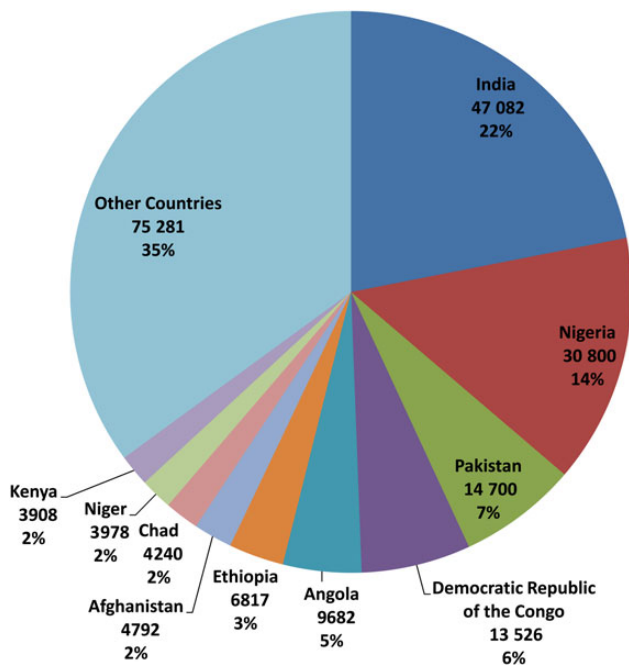


**Figure 2.** Trends in the number of rotavirus deaths (*A*) and the proportion of diarrhea deaths due to rotavirus (*B*) by region, 2000–2013.

## DISCUSSION

We estimated that 37% of the 578 000 diarrheal deaths in children <5 years of age in 2013 were due to rotavirus, resulting in 215 000 rotavirus deaths in this age group. The proportion of diarrheal deaths due to rotavirus decreased only slightly from 43% to 37% over the 14-year study period from 2000 to 2013. However, because the estimated number of diarrheal deaths

declined by more than half during this time period, the number of rotavirus deaths decreased from 528 000 to 215 000. More than 90% of rotavirus deaths in 2013 occurred in 72 low-income and low-middle-income countries eligible for support for rotavirus vaccine procurement from Gavi, the Vaccine Alliance. The majority (56%) of rotavirus deaths occurred in countries of sub-Saharan Africa, the region that also accounted for all 10



**Figure 3.** Countries with the greatest number of rotavirus deaths among children <5 years of age, 2013.

countries in 2013 with rotavirus mortality rates >100 per 100 000. Given its large population size, India had the largest number of estimated rotavirus deaths for a given country, singularly accounting for more than one-fifth of global rotavirus deaths in 2013. With the implementation of rotavirus vaccines beginning in 2012 in several sub-Saharan African countries, and the licensure of a low-cost, locally manufactured rotavirus vaccine in India in early 2014 [23], the impact of vaccination on childhood mortality from rotavirus may soon be more fully realized.

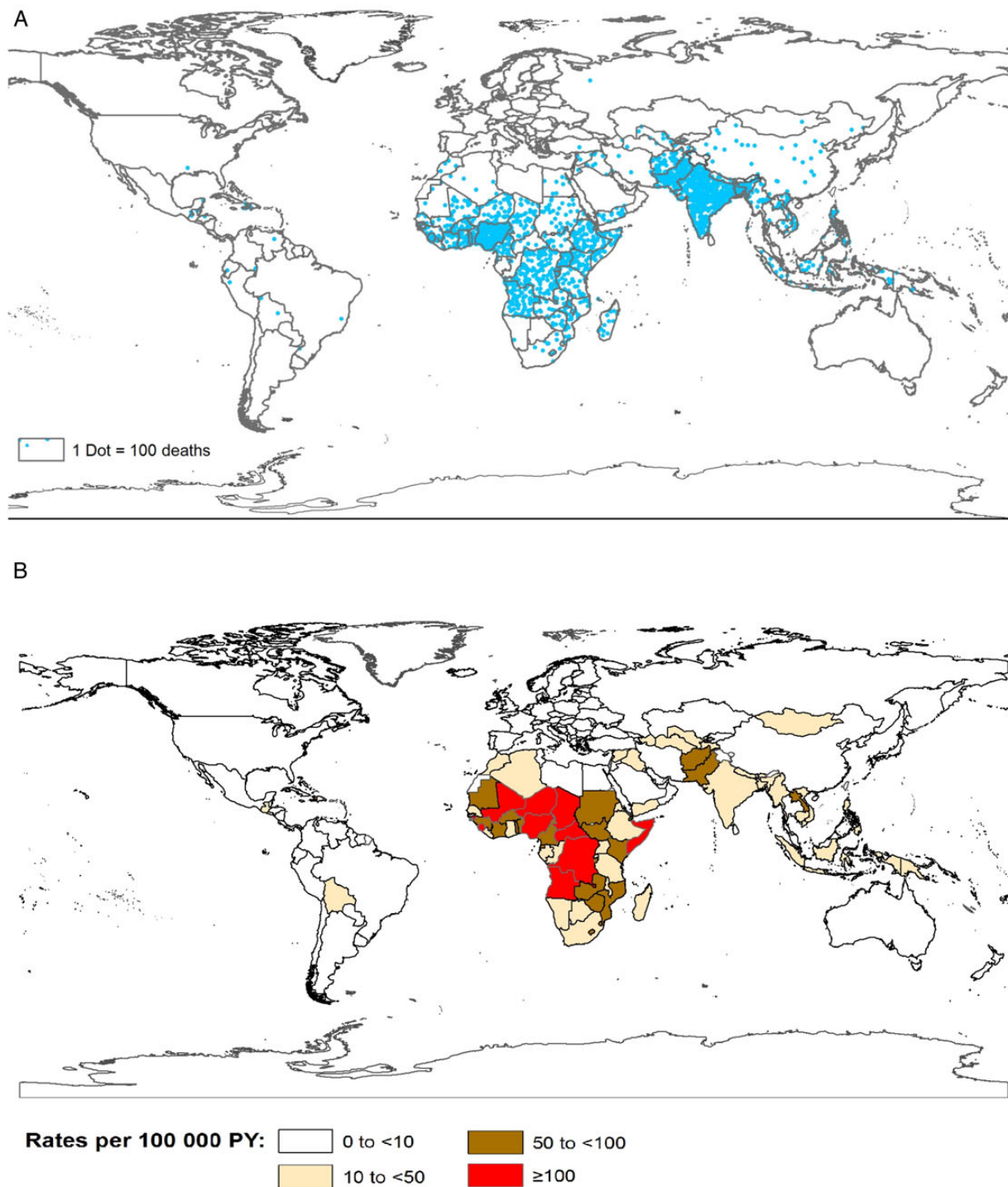
Comparison of the current figures with our own previously published estimates of rotavirus mortality for the year 2004 and 2008 derived using the same methods is difficult [9, 24], largely because of changes in methods and data sources for estimating the overall envelope of diarrhea mortality that we used to derive rotavirus mortality figures over the years [10]. For example, we previously estimated 453 000 rotavirus deaths in 2008, based on the 2010 WHO estimate of 1.2 million diarrheal deaths in children <5 years of age in 2008 [9]. In this analysis, we now estimate 296 000 rotavirus deaths in 2008, based on the updated 2013 WHO estimate of 752 000 diarrheal deaths in children <5 years of age in 2008. However, the proportion of diarrhea deaths due to rotavirus in 2008 was similar for the previous (37%) and current (39%) analyses. The figures presented in this report thus represent the most updated and consistent comparison of trends in diarrhea and rotavirus mortality over the period 2000–2013.

Our estimates of 265 000 (range, 244 000–286 000) rotavirus deaths in 2010, 248 000 (range, 228 000–267 000) rotavirus deaths

in 2011, and 215 000 (range, 197 000–233 000) rotavirus deaths in 2013 are somewhat higher than other contemporary estimates of 173 000 (uncertainty range, 133 100–284 400) rotavirus deaths in 2010 by Lozano et al, 192 700 (uncertainty range, 133 100–284 400) rotavirus deaths in 2011 by Fischer Walker et al, 197 000 (uncertainty range, 110 000–295 000) rotavirus deaths in 2011 by Lanata et al, and 122 000 (uncertainty range, 97 000–152 000) in 2013 by the Global Burden of Disease (GBD) Study in 2013 [11–13, 25] (Table 2). This disparity is largely related to differences in data sources and analytic assumptions for the various studies. For the overall envelope of diarrhea mortality used to estimate rotavirus deaths, we used estimates based on the 2013 Child Health Epidemiology Reference Group (CHERG) diarrhea mortality estimates, whereas Fischer Walker et al and Lanata et al used the 2011 CHERG diarrhea mortality estimates, and Lozano et al and GBD 2013 used their own GBD estimates for diarrhea mortality for the years 2010 and 2013, respectively. The large differences in overall diarrhea mortality envelopes have a substantial impact on rotavirus mortality estimates among various studies.

Another key difference is that the studies of Fischer Walker et al, Lanata et al, and Lozano et al adjusted lower their etiologic fraction of hospitalized diarrhea attributable to rotavirus to account for factors such as mixed infections with other diarrheal pathogens and possible detection of rotavirus in asymptotically infected children [11, 13, 25]. We did not make such adjustments because the recently completed Global Enteric Disease Multi-center Study (GEMS), one of the most comprehensive and up-to-date evaluations of the etiology of childhood diarrheal illness conducted in 4 African and 3 Asian countries, found that nearly all children infected with rotavirus were symptomatic with moderate-to-severe diarrhea [26] and that approximately 90% of cases with moderate-to-severe diarrhea with rotavirus detected by EIA in the stool were attributable to rotavirus. Other studies have also shown that rotavirus is infrequently detected by EIA in stools from healthy children [26–28]. Thus, we assumed that the detection of rotavirus by EIA in children hospitalized with diarrhea was causally related to illness. Although we may be overestimating rotavirus deaths by approximately 10% for not making any adjustments for mixed or asymptomatic infections, laboratory testing by EIA may not detect rotavirus in some children infected by this pathogen if specimens are obtained late in illness or are of insufficient quantity; the resulting underestimation of rotavirus burden may offset, in part or fully, any overestimation from not accounting for coinfection with other pathogens.

Additionally, the GBD 2013 study with the lowest estimate of 122 000 rotavirus deaths in 2013 used the most distinctive counterfactual approach to estimate pathogen-specific diarrhea mortality, incorporating GEMS data into their estimates by calculating etiologic-specific population attributable fractions using the relative risk of pathogens for diarrhea together with



**Figure 4.** Number of rotavirus deaths (A) and rates of rotavirus mortality (B) among children <5 years of age, by country, 2013. Abbreviation: PY, person-years.

the prevalence of the pathogen in patients. Additionally, as GEMS data were only available for 4 African and 3 Asian countries, these attributable fractions had to be extrapolated to all countries globally. Of note, using this counterfactual approach, 41.5% of all childhood diarrhea deaths were of unidentified etiology. Without a more detailed examination of the various

analytic approaches, which is beyond the scope of our study, a proper comparison of our estimates with other studies is not feasible.

The large declines in diarrhea mortality over the past decade are likely largely related to general improvements in sanitation and hygiene; however, the impact of these interventions is not

**Table 2. Comparison of Estimates of Rotavirus Mortality**

Year	Mortality	Lozano et al [11]	Fischer Walker et al [13]	Lanata et al [25]	Global Burden of Disease Study 2013 [12]	Current Estimates
2010	No. of diarrhea deaths	666 000				685 000
	% due to rotavirus	26.0%				38.7%
2011	No. (range) of rotavirus deaths	173 000 (133 100–284 400)				265 000 (244 000–286 000)
	No. of diarrhea deaths		711 800			648 000
2013	% due to rotavirus		27.3%			38.2%
	No. (range) of rotavirus deaths		192 700 (133 100–284 400)	197 000 (110 000–295 000)		248 000 (228 000–267 000)
2013	No. of diarrhea deaths					578 000
	% due to rotavirus					23.5%
	No. (range) of rotavirus deaths					122 000 (97 000–152 000)
						215 000 (197 000–233 000)

likely consistent across pathogens and, in particular, may have less of an impact against pathogens such as rotavirus that are more frequently transmitted person-to-person rather than through contaminated food and water. Thus, the decline in diarrhea mortality may occur equally across all pathogens. This hypothesis is supported by data from a literature review showing that rotavirus caused approximately 22% (range, 17%–28%) of childhood diarrhea hospitalizations in studies published between 1986 and 1999, whereas for studies published from 2000 to 2004, this proportion increased to 39% (range, 29%–45%) [18, 24, 29]. In addition, data from the United States and Mexico showed that as diarrhea-related childhood deaths decreased dramatically in both countries in the latter part of the 20th century, the decline was greatest during the summer months when diarrheal diseases caused by bacteria are more prevalent [30, 31]. Finally, an analysis of longitudinal surveillance data from Dhaka Hospital in Bangladesh showed that the proportion of diarrhea attributable to rotavirus nearly doubled during 2002–2004 compared with 1993–1995 (42% vs 22%;  $P < .001$ ) [32]. Thus, an additional factor that may affect the variability of rotavirus mortality estimates from various studies is the time period for which the rotavirus literature was examined. While we limited studies included in our analysis to those with a midpoint of data collection as 1998–2014 to assess contemporary trends, Lanata et al reviewed studies from 1990 to 2011, Fischer Walker et al reviewed studies from 1980 to 2010, and GBD 2013 reviewed studies with data from 1975 to 2013 as well as administrative databases of hospital discharges that rely on coding rather than specimen testing to assign etiologies.

An additional and unique strength of our approach was that we incorporated rotavirus vaccine use and coverage thresholds into our models. Latin America was the only region that had any appreciable vaccine use during our study period. Rotavirus vaccine introduction began in 2006 with 5 countries in Latin America introducing vaccine into their national immunization programs. By the end of 2011, the last year that rotavirus vaccine could have been introduced to be classified as a vaccine-using country in our analysis, 15 countries that comprised 84% of the region's under-5 population had included rotavirus vaccine in their national immunization programs. Prior to vaccine introduction in the region (2000–2006), the proportion of diarrhea due to rotavirus was 34%–36%. By 2008, the proportion of diarrhea due to rotavirus began to decline and was 26% in 2013. Similarly, the proportion of diarrhea due to rotavirus began to decline in 2012 in developed countries and in countries in Northern Africa where 34% and 18% of the population in these regions, respectively, lived in a country where rotavirus vaccine was available in the national immunization program. Less than 10% of the population had access to rotavirus vaccines in all other regions. Documenting this early decline in Latin America and more recently in developed countries and Northern Africa, but not in other regions where vaccine was not



used, provides further reassurance regarding the validity of our findings.

Our estimates have some limitations. Like other studies, we used the proportion of rotavirus hospitalizations among all-cause diarrhea hospitalizations as a proxy for the contribution of rotavirus to all-cause diarrhea deaths, as laboratory confirmation of causes of diarrheal deaths, particularly those deaths that occur in the community, is rare. However, we do require specimens to be collected through active surveillance meeting a set of strict, standardized criteria for enrollment and testing of specimens and exclude studies using administrative coding or passive surveillance to limit incomplete identification of rotavirus. Countries that have published rotavirus surveillance data or that participated in the WHO-coordinated rotavirus surveillance network may be systematically different in their approach to treatment and care of children with diarrheal disease than countries without such data and thus could influence the proportion of diarrheal hospitalizations due to rotavirus. However, we included data from 774 data points from 90 countries, so we capture a wide variety of study settings in this analysis. Similarly, within countries with such data, hospitals that conduct rotavirus surveillance may not reflect the healthcare-seeking behavior or management that is generalizable at the national level. Also, for our regression model, we used national-level, rather than site-specific, covariates for child mortality and vaccine coverage. While there was some variation in methods in the studies we reviewed (eg, timing of stool specimen collection), and although the number of studies in each region that met the selection criteria varied, we sought to minimize bias by using a standard set of criteria to identify published reports and also applied these same criteria to the network of sentinel hospital-based surveillance sites maintained by WHO that collects data using a standard protocol. Together, these studies provided data from 90 countries representing 86% of the worldwide under-5 population.

While rotavirus vaccine had been introduced into >50 countries worldwide by the end of 2013, the majority of countries currently using rotavirus vaccines are low-mortality countries, so the impact of vaccine use on global estimates of rotavirus mortality has been limited. However, rotavirus vaccines have been shown to have an impact on all-cause diarrhea mortality. Mexico introduced rotavirus vaccines in 2007, and by 2008 had documented a 41% decline in all-cause diarrheal deaths in children <1 year of age [5]. These declines in diarrhea mortality were seen in older age groups in subsequent years and have been sustained through 2011 [33, 34]. Similar declines in diarrhea mortality have been seen in Brazil and Panama [6–8]. These declines are consistent with our estimates of the proportion of diarrhea due to rotavirus before vaccine was implemented, which further validates our findings. As rotavirus vaccine use becomes more widespread, particularly in high-mortality countries, the impact on global mortality rates could be dramatic. Continued monitoring of rotavirus mortality rates and

deaths through rotavirus surveillance will aid in monitoring the impact of vaccination. Further understanding of the differences between the currently available estimates of rotavirus mortality also remains a priority to ensure that obtained estimates of vaccine impact are accurate.

## Notes

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