2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis

*Jacqueline E Tate, Anthony H Burton, Cynthia Boschi-Pinto, A Duncan Steele, Jazmin Duque, Umesh D Parashar, and the WHO-coordinated Global Rotavirus Surveillance Network**

Lancet Infect Dis 2012; 12: 136–41

Published Online October 25, 2011 DOI:10.1016/S1473-3099(11)70253-5

See Comment page 94

*The WHO-coordinated Global Rotavirus Surveillance Network is composed of participating ministries of health, sentinel hospital sites, and the rotavirus laboratory network

Centers for Disease Control and Prevention, Atlanta, GA, USA (J E Tate PhD, J Duque MPH, U D Parashar MBBS); **WHO, Geneva, Switzerland** (A H Burton BS, C Boschi-Pinto MD); **and PATH, Seattle, WA, USA** (A D Steele PhD)

Correspondence to: Dr Jacqueline E Tate, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS-A34, Atlanta, GA 30333 **jqt8@cdc.gov**

Summary

Background WHO recommends routine use of rotavirus vaccines in all countries, particularly in those with high mortality attributable to diarrhoeal diseases. To establish the burden of life-threatening rotavirus disease before the introduction of a rotavirus vaccine, we aimed to update the estimated number of deaths worldwide in children younger than 5 years due to diarrhoea attributable to rotavirus infection.

Methods We used PubMed to identify studies of at least 100 children younger than 5 years who had been admitted to hospital with diarrhoea. Additionally, we required the studies to have a data collection midpoint of the year 2000 or later, to be done in full-year increments, and to assesses diarrhoea attributable to rotavirus with EIAs or polyacrylamide gel electrophoresis. We also included data from countries that participated in the WHO-coordinated Global Rotavirus Surveillance Network (consisting of participating member states during 2009) and that met study criteria. For countries that have introduced a rotavirus vaccine into their national immunisation programmes, we excluded data subsequent to the introduction. We classified studies into one of five groups on the basis of region and the level of child mortality in the country in which the study was done. For each group, to obtain estimates of rotavirus-associated mortality, we multiplied the random-effect mean rotavirus detection rate by the 2008 diarrhoea-related mortality figures for countries in that group. We derived the worldwide mortality estimate by summing our regional estimates.

Findings Worldwide in 2008, diarrhoea attributable to rotavirus infection resulted in 453 000 deaths (95% CI 420 000–494 000) in children younger than 5 years—37% of deaths attributable to diarrhoea and 5% of all deaths in children younger than 5 years. Five countries accounted for more than half of all deaths attributable to rotavirus infection: Democratic Republic of the Congo, Ethiopia, India, Nigeria, and Pakistan; India alone accounted for 22% of deaths (98 621 deaths).

Interpretation Introduction of effective and available rotavirus vaccines could substantially affect worldwide deaths attributable to diarrhoea. Our new estimates can be used to advocate for rotavirus vaccine introduction and to monitor the effect of vaccination on mortality once introduced.

Funding None.

Introduction

Rotavirus infection is the leading cause of severe diarrhoea in young children worldwide.[1] Since 2006, two effective rotavirus vaccines, RotaTeq (Merck and Co, PA, USA) and Rotarix (GSK Biologicals, Rixensart, Belgium), have been licensed, and they are recommended for use in all countries by WHO, particularly in those countries with high diarrhoea-related mortality in children younger than 5 years.[2–6] Substantial declines in morbidity and mortality attributable to rotavirus and all-cause diarrhoea have been recorded in high-income and middle-income countries that have introduced rotavirus vaccines so far.[7–13] Before rotavirus vaccines become more widely used in immunisation programmes, particularly in low-income countries where most deaths attributable to rotavirus infection happen, documenting the baseline number of deaths attributable to rotavirus infection is important. These baseline estimates will help countries assess the potential value of vaccination and measure the effect of vaccines on mortality attributable to rotavirus infection.

By applying the proportion of severe cases of diarrhoea caused by rotavirus infection in children admitted to hospital to the estimated all-cause child deaths attributable to diarrhoea, WHO estimated 527 000 deaths in 2004 (range 475 000–580 000) in children younger than 5 years due to diarrhoea attributable to rotavirus infection.[14] New all-cause child mortality estimates released recently by the Child Health Epidemiology Reference Group of WHO and UNICEF[15] documented an overall decline in the mortality of children younger than 5 years with a change in the number of deaths due to diarrhoea from 1·8 million deaths in 2003 to 1·3 million in 2008.[15,16] WHO estimated that there were 1·24 million deaths due to diarrhoea in children younger than 5 years in 2008. In view of these

For more on **WHO estimates of deaths in children due to diarrhoea in 2008** see http://www.childmortality.org/cmeMain.html

new figures for overall diarrhoea-related deaths, rotavirus-related mortality estimates need updating.

Although overall child diarrhoea-related mortality has declined over the past few years, this decline might not be uniform for all causes that contributed to these deaths. In particular, improvements in sanitation and hygiene have a large effect on diarrhoea caused by bacteria and parasites, which are mainly transmitted through contaminated food and water, and less of an effect on rotavirus diarrhoea, which is transmitted largely through person-to-person contact.[17–21] Thus, the decrease in overall diarrhoea-related mortality might be disproportionately due to decreases in bacterial and parasitic causes of diarrhoea. Indeed, a previous study[22] showed that although diarrhoea-related mortality has declined over the past three decades the proportion of severe diarrhoea attributable to rotavirus has increased. Since this previous study several reports of rotavirus disease burden have been published and the WHO-coordinated Global Rotavirus Surveillance Network has provided additional data on rotavirus disease burden in countries where data was not previously available.

Our objective is to update the rotavirus-related mortality estimate for children younger than 5 years on the basis of a review of recent published work and data from the WHO-coordinated rotavirus surveillance network.[23]

Methods

Search strategy and selection criteria

To estimate the number of deaths attributable to rotavirus infection in 2008, we used the same methods as used in the previous rotavirus mortality estimate[14] and we followed the PRISMA guidelines. We searched PubMed, with the keyword "rotavirus" as our primary search term, to identify studies published between January, 2001, and January, 2011. We did not limit our search by language.

We limited our analysis to studies that met each of our criteria: a data collection midpoint in the year 2000 or later; done in full-year increments; and assessed diarrhoea due

	Description	Member States
Africa		
Afr-D	Africa with high child mortality and high adult mortality	Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, Togo
Afr-E	Africa with high child mortality and very high adult mortality	Botswana, Burundi, Central African Republic, Congo (Brazzaville), Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, Tanzania, Zambia, Zimbabwe
Americas		
Amr-A	Americas with very low child mortality and very low adult mortality	Canada, Cuba, USA
Amr-B	Americas with low child mortality and low adult mortality	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela
Amr-D	Americas with high child mortality and high adult mortality	Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru
Southeast Asia		
Sear-B	Southeast Asia with low child mortality and low adult mortality	Indonesia, Sri Lanka, Thailand
Sear-D	Southeast Asia with high child mortality and high adult mortality	Bangladesh, Bhutan, Burma, India, Maldives, Nepal, North Korea, Timor-Leste
Europe		
Eur-A	Europe with very low child mortality and very low adult mortality	Andorra, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, UK
Eur-B	Europe with low child mortality and low adult mortality	Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Macedonia, Poland, Romania, Slovakia, Tajikistan, Serbia and Montenegro, Turkey, Turkmenistan, Uzbekistan
Eur-C	Europe with low child mortality and high adult mortality	Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Moldova, Russia, Ukraine
Eastern Mediterranean		
Emr-B	Eastern Mediterranean with low child mortality and low adult mortality	Bahrain, Iran, Jordan, Kuwait, Lebanon, Libya, Oman, Qatar, Saudi Arabia, Syria, Tunisia, United Arab Emirates
Emr-D	Eastern Mediterranean with high child mortality and high adult mortality	Afghanistan, Djibouti, Egypt,* Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen
Western Pacific		
Wpr-A	Western Pacific with very low child mortality and very low adult mortality	Australia, Brunei, Japan, New Zealand, Singapore
Wpr-B	Western Pacific with low child mortality and low adult mortality	Cambodia,† China, Cook Islands, Fiji, Kiribati, Laos,† Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea,† Philippines, Samoa, Solomon Islands, South Korea, Tonga, Tuvalu, Vanuatu, Vietnam

We used quintiles of the distribution of child mortality to define very low child mortality (first quintile), low child mortality (second and third quintiles), and high child mortality (fourth and fifth quintiles).[24] *After improvements in child mortality over recent years, Egypt meets criteria for inclusion in subregion Emr-B with low child mortality and low adult mortality. Egypt has been included in Emr-D for the presentation of subregional totals for mortality and burden to ensure comparability with previous editions of The World Health Report and other WHO publications. †Although Cambodia, Laos, and Papua New Guinea meet criteria for high child mortality, they have been included in the Wpr-B subregion with other developing countries of the western Pacific Region for reporting purposes.

Table 1: **Countries by region and mortality group**

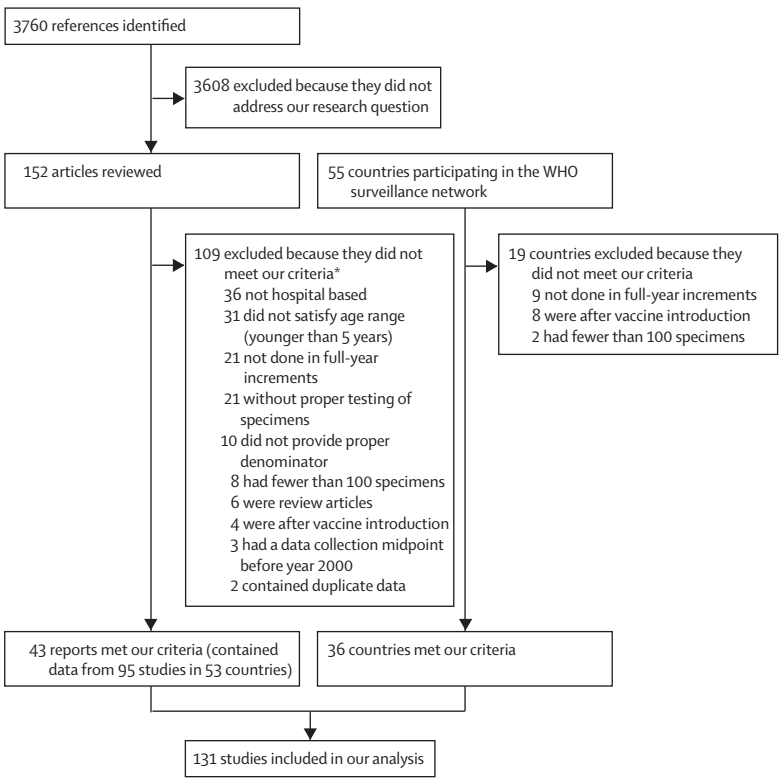

Figure 1: **Study selection**
*Some reports were excluded for more than one reason.

	Number of studies	Number of specimens	Mean detection rate (95% CI)	Number of diarrhoea-related deaths	Number of deaths attributable to rotavirus infection
A	8	7591	49% (34–64)	<1000	<1000
B and C	77	96 349	40% (36–44)	67 000	27 000
D (Asia)	15	13 732	42% (35–48)	452 000	188 000
D (Americas)	3	7567	42% (37–47)	13 000	5000
D and E (Africa)	28	25 933	33% (28–38)	704 000	232 000
Total	131	151 172	..	1 236 000	453 000

For greater detail see the webappendix.

Table 2: **Rotavirus detection rate and deaths due to diarrhoea and rotavirus by WHO child mortality group and region**

See Online for webappendix

to rotavirus infection with an EIA or polyacrylamide gel electrophoresis, tests both sensitive and specific for identifying rotavirus infections, in at least 100 children younger than 5 years who were admitted to hospital with diarrhoea. We also included data from countries that participated in the WHO-coordinated Global Rotavirus Surveillance Network during 2009 and assessed rotavirus-related diarrhoea with EIA in at least 100 children younger than 5 years who were admitted to hospital with diarrhoea.[23] For studies that included data from several countries or several sites within a single country we entered each country and site into our database as a separate study, where possible. For countries that have introduced rotavirus vaccine into their national immunisation programme, we excluded data subsequent to the introduction. Eligible studies were selected and data abstracted by a single author (JET) and reviewed by another author (UDP). For each study that satisfied our criteria we recorded the number of specimens tested, the number of positive results, and the proportion of positive results.

Data analysis

As with the previous assessments of mortality due to rotavirus infection, we constructed five mortality groups on the basis of levels of child mortality (table 1) and region. We assigned countries to one of five groups: group A (countries with very low child mortality), group B and C (countries with low child mortality), group D Americas (countries in the Americas with high child mortality), group D Asia (countries in Asia with high child mortality), and Group D and E Africa (countries in Africa with high child mortality).[14] We used quintiles of the distribution of child mortality to define very low child mortality (first quintile), low child mortality (second and third quintiles), and high child mortality (fourth and fifth quintiles).[24] For each study, we identified the proportion of children admitted to hospital with diarrhoea who tested positive for rotavirus. For each country group we used the DerSimonian–Laird random-effects method[25] to calculate a random-effect mean and 95% CI for the proportion of diarrhoea-related admissions to hospital of children younger than 5 years who tested positive for rotavirus. We used a random-effect mean so that the contribution of each study to the estimated proportion would relate to both the (relative) sample size of the study (within-study variability) and the similarity with other studies (between-study variability). To obtain country-specific estimates of rotavirus-related mortality, we first multiplied the mean and 95% CI of the proportion of diarrhoea attributable to rotavirus for each group by the number of WHO-estimated child deaths caused by diarrhoea for each country in that group. We then summed these country-specific estimates to calculate rotavirus-specific child mortality for each group and worldwide. To derive the 95% CI for our worldwide mortality estimate, we did a bootstrap analysis with 10 000 samples from each stratum and then summed the total number of deaths across the groups. We ordered the resulting total number of rotavirus-related deaths in children younger than 5 years and selected the 250th and 9750th result.

We calculated the rotavirus-specific mortality rates per 100 000 children younger than 5 years with the UN Population Division estimates for the younger than 5 years population in 2008.[5]

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Specimens from 151 172 children younger than 5 years in 65 countries were tested as part of 131 studies that met our inclusion criteria (figure 1, table 2). Rotavirus detection rates ranged from 12% to 68% with a median of 39%. The highest mean detection rate (49%, 95% CI 34–64) was in group A, the countries with the lowest levels of child mortality, and the lowest mean detection rate (33%, 28–38) were in groups D and E in Africa (figure 2).

We estimated that worldwide, each year, rotavirus-related diarrhoea results in 453 000 deaths (95% CI 420 000–494 000) in children younger than 5 years, which accounts for 37% of diarrhoea-related deaths and 5% of all deaths in this age group. About 95% of these rotavirus-related deaths happened in the 72 countries that are eligible to receive GAVI-supported vaccine. National estimates of rotavirus deaths in children younger than 5 years ranged from 99 000 in India to fewer than five deaths in 74 countries. The greatest proportion of deaths was in India (22%). Five countries accounted for more than half of all rotavirus deaths: Democratic Republic of the Congo, Ethiopia, India, Nigeria, and Pakistan (figure 3).

Rotavirus-specific mortality ranged from 518 deaths per 100 000 children younger than 5 years in Afghanistan to less than one death per 100 000 children in 63 countries (figure 4). Five countries (Afghanistan, Burundi, Chad, Mali, and Somalia) had rotavirus-specific mortality greater than 300 deaths per 100 000 children younger than 5 years.

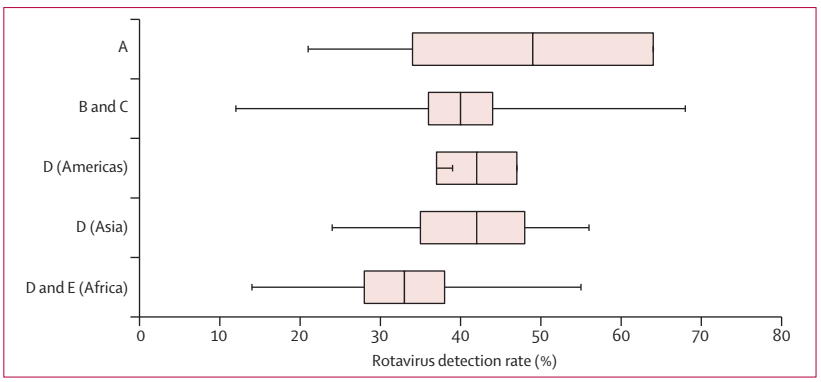

Figure 2: **Rotavirus detection rates by WHO child mortality group and region**
The outer bars represent the range of estimates from the different studies, the box shows the 95% CIs, and the solid line within each box represents the mean rotavirus detection rate. Only three studies met the criteria for inclusion in group D (Americas) and therefore the 95% CI exceeds the range of recorded values.

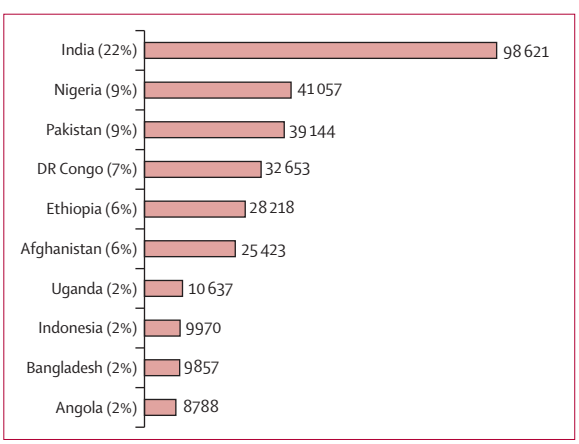

Figure 3: **Countries with the greatest number of rotavirus-related deaths**
Number of deaths due to rotavirus-related diarrhoea (and proportion of the worldwide total).

Discussion

We estimated that, in 2008, rotavirus caused the deaths of 453 000 children younger than 5 years—ie, one of every 260 children born each year will die from diarrhoea caused by rotavirus infection by their fifth birthday. Although the proportion of rotavirus detected in children admitted to hospital with diarrhoea was highest in developed countries, most rotavirus-related deaths were in developing countries in Africa and Asia. India alone accounted for a fifth of these deaths (in part due to the size of its population younger than 5 years), but the greatest concentration of countries with high rates of rotavirus mortality was in sub-Saharan Africa.

Our estimate of deaths due to rotavirus-related diarrhoea in 2008 is somewhat lower than the previous estimate of 527 000 (95% CI 475 000–580 000) deaths in 2004, although the CIs of these estimates overlap. This difference is largely because of an overall decrease in diarrhoea-related deaths in children younger than 5 years from 1·8 million in 2003 to 1·2 million in 2008.[15,16] However, we do not know what proportion of this decrease is due to a true decline in diarrhoea-related mortality and what proportion is due to a change in the methods used to estimate the number of diarrhoea-related deaths. The 32% decrease in all-cause diarrhoea-related deaths is not matched by a decrease of similar size in rotavirus-related deaths, which only declined overall by 14%. This difference is essentially because the published work we assessed for the period 2000 onwards estimates that 37% (95% CI 34–40) of diarrhoea-related deaths were associated with rotavirus compared with 29% (26–32) from the previous review of data from 1990 to 2005. The greater rotavirus detection rate partly offsets the decline in overall diarrhoea-related mortality. For example, in countries with high mortality in Asia, the overall decline in diarrhoea-related mortality from 763 000 to 452 000 deaths was largely compensated for by an increase in the median detection rate of rotavirus from 26% to 42%, resulting in relatively similar rotavirus-related mortality estimates (196 000 in 2004 and 188 000 in 2008).

Some issues should be considered when interpreting our estimates. First, because laboratory confirmation of causes of diarrhoea-related deaths, particularly those in the community, is rare, we had to rely on the proportion of rotavirus-related admissions to hospital in all-cause diarrhoea-related admission as a proxy for the contribution of rotavirus to all-cause diarrhoea-related deaths.

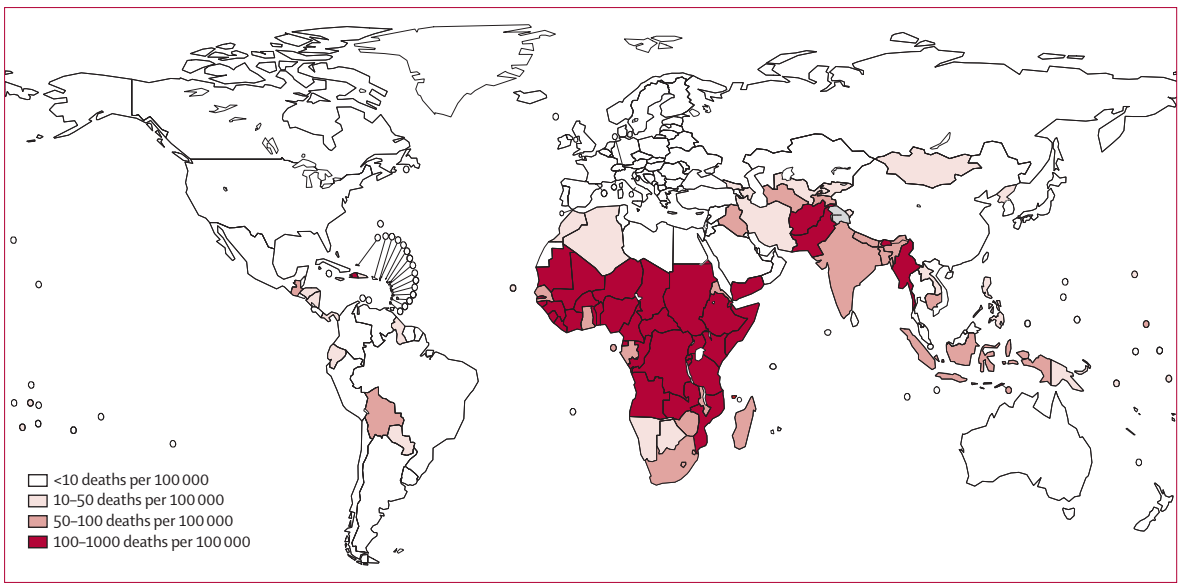

Figure 4: **Rotavirus mortality in children younger than 5 years**

Furthermore, we relied on country-specific diarrhoea-related mortality rates that were generated by a synthesis of several different models.[15] In Mexico, the decline in all-cause diarrhoea-related deaths after the introduction of rotavirus vaccine in 2006[8] is consistent with the number of annual rotavirus-related deaths estimated in our study, suggesting that our method provides a reasonable estimate for rotavirus mortality. As more countries introduce rotavirus vaccine into their national immunisation programmes, the consistency of our estimates with recorded declines in mortality can be further assessed. Second, we assumed that the identification of rotavirus infection in children admitted to hospital with diarrhoea was causally related to the illness. Although molecular methods often identify rotavirus in faecal specimens from healthy children, EIA, the method used in studies we reviewed, identifies rotavirus in healthy children less often.[6] If asymptomatic infections are common, then our estimates of rotavirus-related mortality might be overestimates. Also, most studies included in our analysis tested stool specimens only for rotavirus and did not provide any information about potential co-infections. An ongoing multicountry study[26] assessing stool specimens from children with diarrhoea and from healthy children will provide more information into the frequency of asymptomatic and co-infections. Finally, countries that have published data on rotavirus-related admissions to hospital or that participated in the WHO-coordinated surveillance network might be systematically different in their approach to treatment and care of children with diarrhoeal disease than countries without data, and thus could affect the proportion of diarrhoea-related admissions due to rotavirus. Similarly, hospitals that undertake rotavirus surveillance might not show the health-care seeking behaviour or management that is generalisable at the national level. Although some variation in methods in the studies we reviewed (eg, criteria for enrolment, timing of faecal specimen collection) could have affected our findings and the number of studies in each group that met the selection criteria varied, we used a standard set of criteria to identify published reports and also included data from a network of sentinel hospital-based surveillance sites maintained by WHO that collects data with a standard protocol. Together, these studies provided data from 65 countries representing 69% of the worldwide population of children younger than 5 years. Additionally, the narrow 95% CIs of the rotavirus detection rates suggest that the proportion of diarrhoea due to rotavirus was relatively stable across groups.

Introduction of effective and available rotavirus vaccine could have a substantial effect on diarrhoea-related deaths worldwide. In 2009, WHO expanded its recommendation for rotavirus vaccine use to include all countries worldwide, with a particular emphasis on countries with high diarrhoea-related mortality.[4] However, so far, rotavirus vaccine has largely been introduced only in countries with low diarrhoea-related mortality. The efficacy and effectiveness of rotavirus vaccines is lower in developing-country than in developed-country settings[27–29] and therefore vaccine introduction should be in conjunction with efforts to strengthen health-care systems.[4] Introduction of rotavirus vaccine in developing countries will probably have a substantial effect on worldwide rotavirus-related mortality because of the large number of diarrhoea-related deaths caused by rotavirus infection in developing countries. GAVI cofinancing of vaccine introduction will play a key part in the reduction of mortality due to diarrhoea associated with rotavirus infection, because 95% of rotavirus-related deaths are in countries that are eligible for GAVI support. As more

countries introduce rotavirus vaccine into their national immunisation programmes, continued surveillance is crucial to update estimates of rotavirus-related mortality, including the age distribution of these deaths, and to measure the effect of vaccines and possible changes in the diversity of co-circulating rotaviruses.

Contributors

JET, AHB, CB-P, and UDP created and designed the study. JET and JD collected the data. JET did the data analysis. JET, AHB, CB-P, ADS, AM, JD, and UDP interpreted the data. JET, AHB, and UDP drafted the report. JET, AHB, CB-P, ADS, AM, JD, and UDP critically revised the report.

Conflicts of interest

ADS's institution received money from the Bill & Melinda Gates Foundation to host a meeting in February, 2011, to discuss rotavirus-related mortality estimates. JET, AHB, CB-P, ADS, and UDP attended this meeting. ADS's institution received money from the Sabin Institute to support travel to a typhoid global strategy meeting. AHB's institution receives money from the GAVI Alliance, national governments (Member States), the US Centers for Disease Control and Prevention, the UN Foundation, and the Bill & Melinda Gates Foundation to support its mission.

Acknowledgments

The findings and conclusions of this report are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention. We thank the following countries who provided data through the WHO-coordinated Global Rotavirus Surveillance Network of participating ministries of health, sentinel hospital sites, and the rotavirus laboratory network: Afghanistan, Azerbaijan, Burma, Cameroon, Chile, China, Egypt, Ethiopia, Fiji, Georgia, Ghana, Guatemala, Guinea-Bissau, Iraq, Kenya, Laos, Libya, Mongolia, Morocco, Nepal, Pakistan, Papua New Guinea, Paraguay, Moldova, Sudan, Surinam, Syria, Togo, Tunisia, Uganda, Ukraine, Tanzania, Vietnam, Yemen, Zambia, Zimbabwe.

References

1 Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis* 2003; **9:** 565–72.

2 Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006; **354:** 11–22.

3 Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006; **354:** 23–33.

4 WHO. Rotavirus vaccines: an update. *Wkly Epidemiol Rec* 2009; **84:** 533–37.

5 WHO. Meeting of the immunization Strategic Advisory Group of Experts, April 2009—conclusions and recommendations. *Wkly Epidemiol Rec* 2009; **84:** 220–36.

6 WHO. Meeting of the Strategic Advisory Group of Experts on immunization, October 2009—conclusions and recommendations. *Wkly Epidemiol Rec* 2009; **84:** 517–32.

7 Curns AT, Steiner CA, Barrett M, Hunter K, Wilson E, Parashar UD. Reduction in acute gastroenteritis hospitalizations among US children after introduction of rotavirus vaccine: analysis of hospital discharge data from 18 US states. *J Infect Dis* 2010; **201:** 1617–24.

8 Richardson V, Hernandez-Pichardo J, Quintanar-Solares M, et al. Effect of rotavirus vaccination on death from childhood diarrhea in Mexico. *N Engl J Med* 2010; **362:** 299–305.

9 Yen C, Armero Guardado JA, Alberto P, et al. Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccination in El Salvador. *Pediatr Infect Dis J* 2011; **30** (1 suppl)**:** S6–10.

10 Quintanar-Solares M, Yen C, Richardson V, Esparza-Aguilar M, Parashar UD, Patel MM. Impact of rotavirus vaccination on diarrhea-related hospitalizations among children <5 years of age in Mexico. *Pediatr Infect Dis J* 2011; **30** (1 suppl)**:** S11–15.

11 Molto Y, Cortes JE, De Oliveira LH, et al. Reduction of diarrhea-associated hospitalizations among children aged <5 years in Panama following the introduction of rotavirus vaccine. *Pediatr Infect Dis J* 2011; **30** (1 suppl)**:** S16–20.

12 Braeckman T, Van Herck K, Raes M, Vergison A, Sabbe M, Van Damme P. Rotavirus vaccines in Belgium: policy and impact. *Pediatr Infect Dis J* 2011; **30** (1 suppl)**:** S21–24.

13 Buttery JP, Lambert SB, Grimwood K, et al. Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule. *Pediatr Infect Dis J* 2011; **30** (1 suppl)**:** S25–29.

14 Parashar UD, Burton A, Lanata C, et al. Global mortality associated with rotavirus disease among children in 2004. *J Infect Dis* 2009; **200** (suppl 1)**:** S9–15.

15 Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* 2010; **375:** 1969–87.

16 Bryce J, Boschi-Pinto C, Shibuya K, Black RE. WHO estimates of the causes of death in children. *Lancet* 2005; **365:** 1147–52.

17 Rodriguez WJ, Kim HW, Brandt CD, et al. Longitudinal study of rotavirus infection and gastroenteritis in families served by a pediatric medical practice: clinical and epidemiologic observations. *Pediatr Infect Dis J* 1987; **6:** 170–76.

18 Velazquez FR, Matson DO, Calva JJ, et al. Rotavirus infections in infants as protection against subsequent infections. *N Engl J Med* 1996; **335:** 1022–28.

19 Black RE, Lopez de Romana G, Brown KH, Bravo N, Bazalar OG, Kanashiro HC. Incidence and etiology of infantile diarrhea and major routes of transmission in Huascar, Peru. *Am J Epidemiol* 1989; **129:** 785–99.

20 Simhon A, Mata L, Vives M, et al. Low endemicity and low pathogenicity of rotaviruses among rural children in Costa Rica. *J Infect Dis* 1985; **152:** 1134–42.

21 Zaki AM, DuPont HL, el Alamy MA, et al. The detection of enteropathogens in acute diarrhea in a family cohort population in rural Egypt. *Am J Trop Med Hyg* 1986; **35:** 1013–22.

22 Parashar UD, Gibson CJ, Bresse JS, Glass RI. Rotavirus and severe childhood diarrhea. *Emerg Infect Dis* 2006; **12:** 304–06.

23 WHO. Global rotavirus information and surveillance bulletin reporting period: January through December 2009. http://www.who.int/nuvi/surveillance/HQBulletin_Rota_2009_final.pdf (accessed April 21, 2011).

24 WHO. List of member states by WHO region and mortality stratum. http://www.who.int/whr/2004/annex/topic/en/annex_member_en.pdf (accessed Aug 8, 2011).

25 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7:** 177–88.

26 University of Maryland School of Medicine. The Global Enterics Multi-Center Study (GEMS). http://medschool.umaryland.edu/GEMS/default.asp (accessed Aug 8, 2011).

27 Patel M, Pedreira C, De Oliveira LH, et al. Association between pentavalent rotavirus vaccine and severe rotavirus diarrhea among children in Nicaragua. *JAMA* 2009; **301:** 2243–51.

28 Madhi SA, Cunliffe NA, Steele D, et al. Effect of human rotavirus vaccine on severe diarrhea in African infants. *N Engl J Med* 2010; **362:** 289–98.

29 Zaman K, Dang DA, Victor JC, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial. *Lancet* 2010; **376:** 615–23.