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

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Abstract

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 assess 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 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.

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. 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. 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. 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. New all-cause child mortality estimates released recently by the Child Health Epidemiology Reference Group of WHO and UNICEF 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. WHO estimated that there were 1·24 million deaths due to diarrhoea in children younger than 5 years in 2008. In view of these
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.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 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.

**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 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 to rotavirus by year of death.

**Data sources**

We reviewed publications identified from PubMed and search terms were developed in consultation with an external panel of experts. We searched MEDLINE (1946 to 2011), international databases (Embase, BIOSIS, Cochrane, CINAHL), and databases from international organisations (World Health Organization [WHO], UNICEF, UNICEF-ICEF). We also searched conference proceedings and annual reports of the WHO’s Global Rotavirus Surveillance Network.

We retrieved 3082 citations; 2206 were unique and 1102 after duplicate removal. We reviewed titles and abstracts, assessed criteria: a data collection midpoint in the year 2000 or later; done in full-year increments; and assessed diarrhoea due torotavirus by year of death.

We obtained full texts for 2127 of these studies and we excluded 703 on the basis of title and abstract review. Of the 1424 full-text articles, we excluded 1028 after title and abstract review; 295 due to lack of rotavirus-related mortality data and 14 due to other reasons. We included 374 studies.

**Data abstraction and input**

We obtained data from the studies included in the analysis. We provided key information for each study, including year, geographical region, and the number of deaths attributable to rotavirus. We also provided the number of deaths attributable to diarrhoea in general and the proportion attributable to rotavirus.

We confirmed the number of deaths attributable to rotavirus for each year using the methods described above. We used the data from the studies included in the analysis to estimate the number of deaths attributable to rotavirus in 2008.

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). 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.
55 countries participating in the WHO surveillance network

3608 excluded because they did not address our research question

138 articles reviewed

3608 references identified

352 articles reviewed

409 excluded because they did not meet our criteria
  36 not hospital based
  31 did not satisfy age range (younger than 5 years)
  21 not done in full-year increments
  21 without proper testing of specimens
  10 did not provide proper denominator
  8 had fewer than 100 specimens
  6 were review articles
  4 were after vaccine introduction
  3 had a data collection midpoint before year 2000
  2 contained duplicate data

36 countries met our criteria

131 studies included in our analysis

43 reports met our criteria (contained data from 95 studies in 53 countries)

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). 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). 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 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.

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.

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 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).
Furthermore, we relied on country-specific diarrhoea-related mortality rates that were generated by a synthesis of several different models. In Mexico, the decline in all-cause diarrhoea-related deaths after the introduction of rotavirus vaccine in 2006 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. 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 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 diarrhoea-related 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.

Figure 4: Rotavirus mortality in children younger than 5 years

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. 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 and therefore vaccine introduction should be in conjunction with efforts to strengthen health-care systems. 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 rotavirus strains.

**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 support its mission. 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 networks: 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, Suriname, Syria, Togo, Tunis, Uganda, Ukraine, Tanzania, Vietnam, Yemen, Zambia, Zimbabwe.

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