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Rotavirus-specific and Overall Diarrhea Mortality in Chinese Children Younger than 5 Years:

2003 to 2012

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Abstract

Background—During the past decade, substantial declines in overall childhood mortality from diarrhea have been documented among Chinese children, but the last detailed assessment of rotavirus-specific mortality in China was conducted in 2002. To provide policy makers with up-to-date information, we examined rotavirus-related mortality in children <5 years of age in China during 2003–2012.

Methods—We obtained mortality rates for children <5 years of age from the Chinese Health Statistic Yearbook; these figures were multiplied by the proportion of deaths in this age group attributable to diarrhea from the Chinese Maternal and Child Mortality Surveillance to obtain estimates of diarrhea deaths in children <5 years of age. To estimate rotavirus deaths, diarrhea death estimates were multiplied by the detection rate of rotavirus in children hospitalized with diarrhea from the Viral Diarrhea Surveillance System in China and from peer-reviewed literature.

Results—From 2003 to 2012, a total of 127,539 deaths from diarrhea were reported among Chinese children <5 years of age, of which an estimated 53,559 (42%) had illness attributable to rotavirus. Comparing 2003 to 2012, the annual number of deaths from rotavirus diarrhea

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JZ, CY, DP, BJ, JT and UP designed the study. JZ collected and analyze data and drafted the report. DP, CY and UD modified the report. BJ and JT reviewed the report. DZ, XP, JY ZC, NL, JS and XR provided a part of surveillance data and published literature. The authors have no funding or conflicts of interest to disclose.

decreased by 74% (from 10,531 to 2,791, respectively) and the mortality rate fell 74% (from 0.66 to 0.17 deaths per 1000 live births, respectively). Ninety-three percent of all rotavirus deaths occurred in rural areas, where mortality rates (0.33 deaths per 1000 live births in 2012) were 11 times greater than in urban areas (0.03 deaths per 1000 live births in 2012).

Conclusions—Rotavirus diarrhea mortality has substantially declined in the past decade in Chinese children. The vast majority of rotavirus deaths occurred in rural areas. There is potential value in using rotavirus vaccine interventions in rural areas to further reduce mortality from this disease.

Keywords

all-cause diarrhea death; rotavirus-specific diarrhea death; mortality; children; China

Diarrhea is a leading cause of death among children <5 years of age worldwide¹ and rotavirus gastroenteritis is the single leading etiologic agent of severe childhood diarrhea globally.² Reducing diarrhea deaths is an important strategy toward achieving the United Nations Millennium Development Goals to reduce child mortality.¹ A 2008 World Health Organization (WHO)/United Nations Children Fund (UNICEF) study on causes of childhood death demonstrated a 71% reduction in the overall mortality rate in children <5 years of age (from 64.6 to 18.5 per 1000 live births) in China during 1990–2008.³ During this period, mortality from childhood diarrhea declined 91% from 4.3 per 1000 in 1990⁴ to 0.38 per 1000 in 2008. While diarrhea mortality has declined substantially during the past 2 decades, the most recent detailed assessment of mortality associated with rotavirus in Chinese children was conducted more than a decade ago in 2002.⁵ This assessment estimated that 13,400 children under 5 years died from rotavirus in 2002, with 70% of these deaths occurring in rural areas.⁵

A locally manufactured, Lanzhou lamb-derived rotavirus vaccine (LLR; Lanzhou Institute of Biological Products) has been available in China since 2001,⁶ but it is not included in China's Expanded Program on Immunization). In addition, the 2 rotavirus vaccines recommended for global use by WHO—Rotarix (Glaxo-SmithKline Biologicals, Rixensart, Belgium) and RotaTeq (Merck & Company Incorporated, Whitehouse Station, New Jersey)—have not yet been introduced in China, and additional candidate rotavirus vaccines are being developed by Chinese vaccine manufacturers. Given these developments, there is a need for updated estimates of rotavirus mortality in Chinese children for policy makers to assess the potential life-saving benefits of implementing rotavirus vacci-nation. To better understand the rotavirus-specific disease burden among Chinese children, we estimated the mortality rate of acute rotavirus gastroenteritis in children <5 years of age from 2003 to 2012 using data from Chinese surveillance systems and published literature.

METHODS

Data Sources

To estimate the burden of rotavirus deaths in China from 2003 to 2012, we obtained the following 4 key pieces of information: the size of the birth cohort; overall mortality rates for

children <5 years of age; the proportion of <5 deaths attributable to diarrhea and the proportion of childhood diarrhea hospitalizations attributable to rotavirus gastroenteritis.

Birth Cohort and <5 Mortality

We obtained information regarding live birth cohorts and national mortality rates for children <5 years of age for each year from 2003 to 2012 from the Chinese Health Statistics Year-book (2013)⁷ and the Statistical Bulletin of China's Development of Health and Family Planning (2013).⁸ To further determine the proportion of deaths occurring in urban versus rural areas, we obtained percentages of urban and rural populations from the Chinese Statistics Yearbook (2013).⁹ Finally, we obtained province-specific live birth and mortality rate data for 2011, the latest year with available data, from the Chinese Statistics Yearbook (2013)¹⁰ and published data.^{4,10–12}

Proportion of <5 Mortality Attributable to Diarrhea

Mortality surveillance among children <5 years of age in China is based on a population-based surveillance system, the Chinese Maternal and Child Mortality Surveillance (MCMS). 10–12 Surveillance counties and districts distributed across 31 provinces/ autonomous regions/municipalities provided mortality data for deaths in children <5 years of age. Cause-of-death was classified using the International Classification of Diseases, 9th Clinical Module (ICD-9-CM) codes.

The proportion of all <5 mortality that was assigned ICD-9-CM codes for diarrhea of determined etiology [bacterial (001 to 005, 008.0 to 008.5), parasitic (006 to 007) and viral (008.6 to 008.8)] and diarrhea of undetermined etiology, including that presumed to be infectious (009.0 to 009.3) and noninfectious (558.1 to 558.9) was abstracted from the MCMS for each year during 2003–2012. Since the 2008 figures were likely impacted by the Wenchuan earthquake that occurred on May 12, 2008, causing more than 70,000 deaths, we used the average of proportions of <5 mortality attributable to diarrhea for 2007 and 2009 as a proxy figure for 2008.

Detection Rates of Rotavirus in Children Hospitalized with Diarrhea

The Viral Diarrhea Surveillance System (VDSS), coordinated by the Chinese Center for Disease Control and Prevention since 1998, examines the proportion of diarrhea hospitalizations attributable to rotavirus among children <5 years of age in 17 Chinese provinces/autonomous regions/municipalities (Beijing, Hebei, Neimenggu, Shanxi, Jilin, Hunan, Anhui, Jiangsu, Shanghai, Henan, Sichuan, Fujian, Guangxi, Guangdong, Gansu, Xinjiang and Yunnan). As part of the VDSS, sentinel hospitals in each of the 17 provinces/autonomous regions/municipalities test stool samples for children <5 years of age who have been hospitalized with diarrhea. These stool samples are tested for rotavirus using a commercial enzyme immunoassay (IDEIA Rotavirus) in the laboratories of provincial and prefectural/city CDC in the VDSS.

National Mortality Rates of Children <5 Years Old

We obtained information regarding national all-cause mortality rates for children <5 years of age for each year from 2003 to 2012 from the Chinese Health Statistics Yearbook (2013)⁷

and the Statistical Bulletin of China's Development of Health and Family Planning (2012).⁸ Also included in these sources are national data on socioeconomics, health services, and water and sanitation resources.

Analysis

To calculate the <5 all-cause mortality rate and diarrhea mortality rate (defined as the number of diarrheal deaths in children <5 year of age per 1000 live births), we first estimated the annual number of child deaths for each year during 2003–2012 by multiplying the <5 mortality rate by the number of live births in the population. We then estimated the annual number of diarrheal deaths by multiplying the total number of child deaths by the proportion of deaths recorded as attributable to diarrhea according to the MCMS for that year. Using methods similar to those used by the WHO Child Health Epidemiology Reference Group, we estimated the number of deaths from rotavirus diarrhea in children <5 years of age by multiplying the number of diarrheal deaths by the proportion of laboratory-confirmed rotavirus cases among hospitalized children with diarrhea. Finally, we calculated the annual rotavirus-associated mortality rate by dividing the number of rotavirus-related deaths in a given year by the number of live births that year.

To stratify results by urban/rural location, we distributed the number of rotavirus deaths by the proportion of the population that lived in each location type for each year from 2003 to 2012. We then compared the rotavirus mortality rates between urban and rural areas in these years using Fisher's exact test.

We also examined the number of rotavirus deaths and mortality rates by province for the year 2011. Based on available provincial birth cohort data in 2011, figures for diarrhea mortality were derived separately for each provincial estimate from the Chinese Health Statistics Yearbook (2013) and other published literature, ^{16–18} and were then multiplied by province-specific rotavirus detection rates from the VDSS to estimate rotavirus deaths for each province. For Tianjin, Jiangxi and Guizhou provinces, which are not included in the VDSS, we applied positive rates of rotavirus from the published literature. ^{19–21} For the 11 other non-surveillance sentinel provinces, we estimated rotavirus positivity rates using the rate from a neighboring province included in the VDSS.

Based on a dynamic series model, we calculated the yearly average increasing speed (AIS) from 2003 to 2012 between urban and rural areas. The AIS reflects the average increase or decrease in the proportion of rotavirus disease per year from 2003 to 2012. The following formula was used:

$$AIS = \left(\overline{X}_g - 1\right) \times 100\% = \left(\sqrt[n]{\prod_{i=1}^n x_i} - 1\right) \times 100\%$$
$$= \left(\sqrt[n]{\frac{a_n}{a_1}} - 1\right) \times 100\%$$

 X_g was defined as the average develop speed of the number or the rate (a) per year in a period time and calculated by multiply each ratio (χ) The serial years in dynamic series model is i (1 to n). χ is defined as the ratio [the number or rate in the year (n + 1)/the number or rate in the year (n)].

RESULTS

Trends in Deaths from All-cause Diarrhea and Rotavirus Diarrhea from 2003 to 2012

From 2003 to 2012, a total of 127,539 deaths from diarrhea were reported among Chinese children <5 years of age, of whom an estimated 42% (53,559) had illness attributable to rotavirus. Comparing 2003 to 2012, the annual number of deaths from all-cause diarrhea decreased by 68.1% (from 23,222 in 2003 to 7,406 in 2012), and the annual number of deaths from rotavirus diarrhea decreased by 73.5% (from 10,531 in 2003 to 2791 in 2012; Fig. 1).

Of the 53,559 rotavirus diarrhea deaths, it is estimated that 92.7% (49,649) occurred in rural areas and 7.3% (3910) occurred in urban areas. From 2003 to 2012, there was a 75% decrease in the number of annual rotavirus deaths (from 10,164 in 2003 to 2539 in 2012) in rural areas. However, in urban areas, the annual number of rotavirus-attributable deaths was relatively stable during this period (367 in 2003 and 252 in 2012).

Mortality Rates from All-cause Diarrhea and Rotavirus Diarrhea from 2003 to 2012

From 2003 to 2012, the mortality rate from all-cause diarrhea declined by 69%, from 1.45 per 1000 live births in 2003 to 0.45 deaths per 1000 live births in 2012 (Fig. 2). In rural areas, the mortality rate declined by 65.5%, from 1.74 per 1000 live births in 2003 to 0.60 deaths per 1000 live births in 2012. In urban areas, the mortality rate declined by 33.3%, from 0.12 per 1000 live births in 2003 to 0.08 deaths per 1000 live births in 2012. During this same time, the mortality rate from rotavirus diarrhea declined by 74.2%, from 0.66 per 1000 live births in 2003 to 0.17 deaths per 1000 live births in 2012 (Fig. 2). In rural areas, the rotavirusspecific mortality rate declined by 69.2%, from 1.07 per 1000 live births in 2003 to 0.33 deaths per 1000 live births in 2012. In urban areas, the rotavirus-specific mortality rate declined by 50%, from 0.06 per 1000 live births in 2003 to 0.03 deaths per 1000 live births in 2012.

For each year from 2003 to 2012, the annual mortality rate for rotavirus-related diarrhea was significantly higher in rural areas compared with urban areas (P < 0.001).

Rotavirus Diarrhea Mortality by Province in 2011

The number of deaths and mortality rates attributable to rotavirus diarrhea in 31 provinces were examined (Fig. 3). Ten provinces/autonomous regions including Xinjiang Autonomous, Hebei Province, Jiangxi Province, Shandong Province, Sichuan Province, Henan Province, Henan Province, Hunan Province, Anhui Province, Yunnan Province and Hubei Province accounted for about 62.8% of the total number of deaths from rotavirus.

The mortality rates in 31 provinces ranged from 0.006 per 1000 live births to 0.70 per 1000 live births, with the highest rates occurring in Xinjiang Autonomous (0.70/1000 live births), Tibet Autonomous (0.33/1000 live births), Jiangxi Province(0.28/1000 live births), Qinghai Province (0.27/1000 live births) and Hainan Province (0.26/1000 live births; Fig. 3). The highest rotavirus-attributable mortality was found in the far northwestern, western,

northeastern and southern provinces. High rotavirus-attributable mortality was also found in some northeastern and southern provinces (Fig. 4).

Average Annual Changes in Rotavirus Mortality and Possible Impact Factors

Annual rates of all-cause mortality, all-cause diarrhea, rotavirus-related mortality and rotavirus positivity in hospitalized patients <5 years of age for urban and rural areas are shown in Table 1. Also included in Table 1 are potential impact factors including population, health staff per 10,000 persons, health care cost per person per year, as well as tap water supply and sanitary toilet use.

The all-cause mortality rate and all-cause diarrhea mortality, as well as rotavirus-associated mortality rate and rotavirus positivity among diarrhea hospitalizations decreased on average by 8.7%, 12.1%, 13.9% and 2.0% per year from 2003 to 2012, respectively. However, population, health staff per 10,000 persons, health care cost per person per year, tap water supply and sanitary toilet use increased overall. The all-cause diarrhea mortality in urban and rural areas decreased 0.5% and 11.1% per year, respectively. Furthermore, rotavirus-associated mortality decreased both in urban and rural areas by 5.5% and 13.2%, respectively.

DISCUSSION

We found consistent and marked declines in rotavirusspecific and overall diarrhea mortality in Chinese children during our study period from 2003 to 2012. The rotavirus-attributable diarrhea mortality rate declined 74% from 2003 to 2012, similar to trends in overall diarrhea mortality and the all-cause mortality rate among children <5 years during 1990–2008, as reported by WHO/UNICEF's Child Health Epidemiology Reference Group. ^{3,4} Rotavirus-associated mortality had a greater rate of decrease than all-cause childhood mortality and all-cause diarrheal mortality. The overall declining trend of childhood mortality is likely related, in large part, to the rapid socioeconomic development and improvements in medical care and public health systems.

Our estimate of 2791 rotavirus deaths among Chinese children in 2012 is substantially lower than previously published estimates for earlier time periods—Yee et al⁵ estimated 13,400 deaths from rotavirus in 2002; Parashar et al² estimated 34,553 deaths caused by rotavirus based on studies from 1986 to 2000 and Orenstein et al. estimated more than 35,000 childhood deaths due to rotavirus from 1983 to 2005.²² The large difference between our estimates and those from older studies likely reflects the rapidly declining mortality from overall diarrhea and rotavirus over the past 2 decades in China. However, rotavirus, causing approximately 2800 child deaths in 2012, remains a notable and vaccine-preventable cause of mortality in China.

The rotavirus death estimates in urban areas and rural areas in 2012 were 252 cases and 2539 cases, respectively, with average annual decline over this decade of 5.49% in urban areas and 13.2% in rural areas. While it is possible that improvements in health care service capacity, availability of clean water, and sanitary toilet use contributed to the rapid decrease of diarrhea mortality in rural areas, nevertheless, the vast majority of rotavirus deaths (92%)

occurred in rural areas, with a 10–20 times greater mortality in rural versus urban provinces throughout the study period. Therefore, 1 potential intervention to reduce child mortality due to rotavirus in China may be to ensure that rural children and their families have access to rotavirus vaccines.

Our results show a disparity in the rates of rotavirus diarrhea mortality between provinces. Furthermore, approximately 40% of China's rotavirus-associated childhood deaths occurred in just 5 provinces (or autonomous regions), located in the far northwestern, western and southern regions of China. These data indicate that it is important to improve coverage of rotavirus vaccines, access to medical services, and health education to parents to further reduce deaths from rotavirus diarrhea in these areas.

Some limitations should be noted. It is possible that the proportion of deaths due to rotavirus diarrhea may not exactly match the proportion of severe diarrhea hospitalizations attributable to rotavirus. However, given inherent challenges in obtaining clinical specimens to determine etiologic agents in children who die from diarrhea, other groups including WHO have used similar approaches. ^{5,23,24} In addition, while we used the most reliable and comprehensive local sources of data available, it is possible that some deaths, particularly those in less socioeconomically developed areas, may not have been fully reported.

In conclusion, overall diarrhea-specific and rotavirus childhood mortality in China during the past decade continued declines, but a substantial number of Chinese children continue to die from rotavirus. The vast majority of rotavirus deaths occurred in rural areas. These data illustrate the potential value of using rotavirus vaccine interventions against rotavirus in rural areas, to further reduce mortality from this disease.

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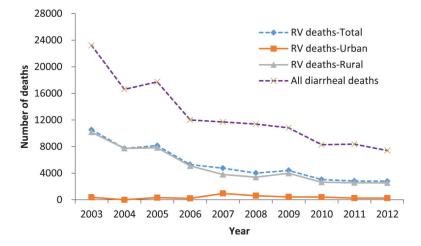


FIGURE 1. Trends in diarrhea deaths and rotavirus-specific diarrhea deaths in children <5 years of age in China, 2003–2012.

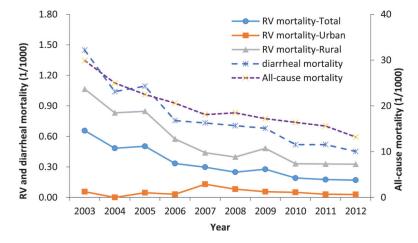


FIGURE 2. Trends in mortality rate from rotavirus-related diarrhea in children <5 years of age in China, overall and by urban/rural location, 2003–2012.

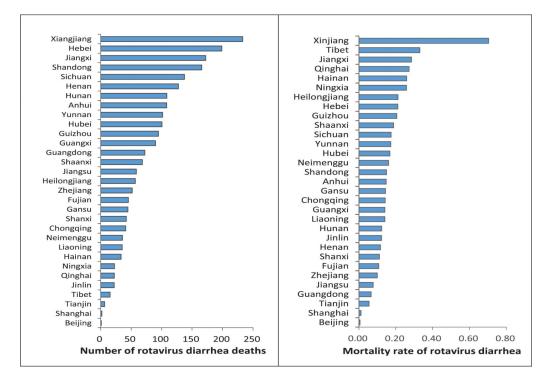


FIGURE 3. The range of deaths and mortality rate from rotavirus diarrhea in children <5 years of age in 2011 by provinces.



FIGURE 4. Geographic distribution of mortality rates from rotavirus diarrhea in children younger 5 years of age in 2011.

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TABLE 1

Average Increasing Speed (AIS) of Mortality Rate and Related Factors in Urban and Rural Areas of China per Year, 2003 to 2012

	Total			Urban Areas			Rural Areas		
	2003	2012	AIS (%)	2003	2012	AIS (%)	2003	2012	AIS (%)
All-cause mortality rate of children <5 years (1/1000)	29.9	13.2	-8.68	14.8	5.9	-9.71	33.4	16.2	-7.72
All-cause diarrheal mortality rate of children <5 years (1/1000)	1.45	0.45	-12.13	0.12	0.08	-0.5	1.74	0.60	-11.11
Rotavirus mortality rate of children <5 years (1/1000)	0.66	0.17	-13.92	0.06	0.03	-5.49	1.07	0.33	-13.2
%Rotavirus positive in inpatient diarrhea patients <5 years	45.35	37.69	-2.04	37.7	25.4	-4.29	48.4	39.57	-2.21
GDP (billion USD)	2227	8516	16.07	-	-	-	-	-	-
Population (million)	1292.27	1354.04	0.52	523.76	711.82	2.93	768.51	642.22	-2.48
Health staff per 10,000 persons	35	49	3.81	49	85	6.31	23	34	4.44
Health cost/person per year (USD)	509.50	2056.57	16.77	1108.91	2969.01	11.56	274.67	1055.89	16.14
%Population of tap water supply	-	-	-	88.8	97.2	1.14	55.2	74.6	2.98
%Sanitary toilet use	-	-	-	-	-		32.3	49.7	7.45

The data of cover population of LLR vaccine each year were not available in urban and rural areas, and a total of 27 million doses of LLR vaccine were used from 2000 to 2012.