Vaccine 32S (2014) A5–A9

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Rotavirus gastroenteritis in India, 2011–2013: Revised estimates of disease burden and potential impact of vaccines

Jacob John[a], Rajiv Sarkar[a], Jayaprakash Muliyil[a], Nita Bhandari[b], Maharaj K. Bhan[c], Gagandeep Kang[a,*]

[a] Christian Medical College, Vellore, India
[b] Society for Applied Studies, New Delhi, India
[c] Ministry of Science and Technology, New Delhi, India

A B S T R A C T

While improvements in oral rehydration use and access to healthcare have contributed to impressive gains in child survival, diarrheal diseases remain the second most important cause of child mortality in India. Pathogen specific disease rates, while key to deciding on the utility of specific public health interventions such as vaccines, are extremely difficult to obtain in developing country settings with less than optimal health access, diagnostic services and information systems.

This study combined disease burden within five cohorts of infants followed up for diarrheal morbidity with data from the nationally representative Indian Rotavirus Surveillance Network and applies rates of rotavirus related events to UNICEF birth and mortality estimates for India. These estimates, while limited by the lack of data from nationally representative population based studies, use methods consistent with those employed by the World Health Organization Child Health Epidemiology Reference Group.

We estimate that 11.37 million episodes of rotavirus gastroenteritis occur each year in India, requiring 3.27 million outpatient visits and 872,000 inpatient admissions when health access is unconstrained, resulting in a need for Rs. 10.37 billion each year in direct costs. An estimated 78,000 rotavirus-associated deaths occur annually of which 59,000 occur in the first 2 years of life. Introduction of a rotavirus vaccine of similar efficacy to the Rotavac in the national immunization program would result in 686,277 fewer outpatient visits, 291,756 fewer hospitalizations and 26,985 fewer deaths each year in India, assuming no indirect effects for the vaccine.

1. Introduction

With concerted effort toward the Millennium Development Goals (MDG) there are now 14,000 fewer child deaths each day across the world as compared to 1990 [1,2]. Improvements in oral rehydration solution (ORS) use and access to healthcare have contributed to impressive gains in diarrheal mortality [3]. Decline in pneumonia and diarrheal mortality have been instrumental in global decline of under five mortality from 88 to 56 per 1000 live births by contributing over 40% of this decline [4,5]. Notwithstanding the gains achieved in the past decade, over 700,000 children die each year of preventable diarrheal diseases in the developing world [2]. Developing countries such as India, where much of the gains in mortality reduction of the past decade have accrued, lack direct estimates of the extent, distribution and determinants of this decline resulting in uncertainty regarding disease specific estimates required for prioritizing public health strategies.

Acute gastroenteritis remains a leading cause of post-neonatal under-five mortality in India contributing about 13% of under-five mortality [5,6]. Rotavirus is the most important cause for severe gastroenteritis in this age group [2,7,8]. Studies in the last decade estimate the annual mortality due to rotavirus in India to be between 90,000 and 153,000 [4,9,10]. Debates on the public health utility of rotavirus specific interventions are, in part, fueled by the heterogeneity of mortality estimates and lack of data on the extent of morbidity associated with the disease. Morbidity, an important component of overall disease burden in developing countries, is under-recognized especially in high mortality settings where morbidity data is not readily available. Even where morbidity data is available, they underestimate true healthcare need, as socio-economic conditions, out of pocket spending and limited health infrastructure are overwhelming determinants of health access [11]. In situations with the highest burden of disease, health information and laboratory systems are inadequately equipped to detect and record etiology specific information.

A newer, more affordable rotavirus vaccine developed through an innovative social partnership may soon be available. Availability of affordable, efficacious vaccines holds promise but challenges policy makers to assess critically the burden of disease and the

* Corresponding author at: Division of Gastrointestinal Sciences, Christian Medical College, Vellore, TN 632004, India. Tel.: +91 416 228 2052.
E-mail address: gkang@cmcvellore.ac.in (G. Kang).

http://dx.doi.org/10.1016/j.vaccine.2014.03.004

anticipated impact in the local conditions. We review the mortality, morbidity and economic burden of rotavirus diarrhea in India in the context of improving child survival and health access, and present estimates of morbidity associated with rotavirus diarrhea from the follow up of five observational cohorts that were offered access to healthcare without fees. This, we believe, represents morbidity not confounded by financial and access to care-related issues and therefore a more accurate measurement of the underlying burden of disease.

2. Methods

2.1. Data sources

We combined data from the Indian Rotavirus Strain Surveillance Network (IRSSN), the Million Death Study (MDS) [13] and statistics compiled by the World Health Organization (WHO) and UNICEF with data from five community-based cohorts to arrive at conservative estimates of the burden of rotavirus diarrhea across the disease spectrum and the economic costs related to the disease.

The IRSSN is a geographically representative, hospital based diarrheal surveillance system that used standardized protocols for enrolment and diagnostic evaluation at eight sites across India during 2005–2009 [12]. This surveillance system sampled diarrheal hospitalization in the sentinel hospitals and provides the proportion of hospitalized diarrhea that was related to rotavirus.

The Million Death Study (MDS), being conducted between 1998 and 2014 by the Registrar General of India and collaborators to determine causes of death in India derives its data from a nationally representative sample of 14 million people in 2.4 million households within the Sample Registration System, a large, routine demographic survey performed by the Registrar General of India. All deaths in the surveyed families have a cause of death assigned according to the International Classification of Diseases Revision 10 and are characterized by age, gender and region [13].

Incidence of diarrhea, diarrheal outpatient visits and hospitalization was obtained from five community-based cohorts that were intensively followed up for enteric diseases till at least two years of age. Three of these cohorts were in Vellore while the fourth was located in an urban slum in Delhi. Four of these cohorts also involved rotavirus testing of diarrheal samples, while a fifth cohort (also based in Vellore) had fortnightly follow-up and healthcare access data but not rotavirus testing of diarrheal samples. The details of the five cohorts are presented in Table 1. The overall rates of gastroenteritis, outpatient visits and hospitalizations due to rotavirus in the first two years of life were obtained as a weighted average from the cohorts. The 95% confidence intervals (95% CI) were calculated using the Byar's approximation of the exact interval for the Poisson distribution [17].

2.2. Rotavirus related diarrheal mortality

The <5 diarrheal mortality rate (defined as the number of diarrheal deaths in children under five per 1000 live births) was obtained by the product of <5 mortality rate of 61 per 1000 live births for India [18] and the proportion of all <5 deaths attributed to diarrhea in the Million Death Study (MDS) [10]

The rotavirus mortality rate was then estimated by applying to the <5 diarrheal mortality rate the proportion rotavirus positive in the IRSSN using methods and assumptions similar to those adopted by the WHO Child Health Epidemiology Reference Group (CHERG) [19,20]. The number of annual rotavirus deaths in India was determined by applying the rotavirus mortality rate to the 2011 birth cohort from UNICEF statistics. These numbers are compared with estimates published previously [9,10].

2.3. Rotavirus related diarrheal morbidity

The data from the five birth cohorts (Table 1) combined provide rotavirus hospitalization rates for children under-two years of age. Applying this rate to the entire under-five population would overestimate the burden, as the risk of rotavirus infection is greatest in the first two years. The proportion of diarrheal hospitalization in the IRSSN that was over three years of age was used as a correction factor to obtain a more conservative 3–5 year and a cumulative <5 year rotavirus hospitalization rate. The number of hospitalizations attributable to rotavirus was obtained by the product of the rotavirus hospitalization rate and the number of children in the 2011 Indian birth cohort.

The ratio of outpatient rotavirus gastroenteritis visits to rotavirus gastroenteritis admission in a phase III clinical trial population was 3.75. Applying this ratio to the number of hospitalized rotavirus gastroenteritis episodes we arrive at the number of rotavirus gastroenteritis outpatient visits. This ratio of ambulatory to hospitalized rotavirus was consistent with unpublished data from CHAD Hospital; a 120 bedded community hospital in Vellore that provides discounted care to a population of about 100,000 within its rural demographic surveillance system.

2.4. Potential impact of rotavirus vaccines

The vaccine efficacy (VE) of three doses of Rotavac®, an oral human-bovine natural reassortant vaccine obtained from a large multicenter phase III trial in India was extrapolated to the risk of rotavirus mortality, hospitalization and outpatient visits to determine the number of deaths, hospitalizations and outpatient visits potentially averted. Vaccine efficacy against severe rotavirus gastroenteritis, rotavirus hospitalization and all rotavirus gastroenteritis were used to calculate impact against rotavirus mortality, rotavirus hospitalization and rotavirus outpatient visits respectively. Risk (defined as the probability of event between 4 months and 5 years) is estimated by the expression cumulative risk = $(1 - \exp^{(-\sum \text{rate}^{*}\Delta t)})$, where 'rate' refers to event rate and 'Δt' the time interval. For estimating the absolute risk of rotavirus related events in the 4 month to 5 year period, we first estimated the event rate for the first two years of life as a weighted average from the cohort and applied this to the four months to two year period to obtain risk estimates for the corresponding period. We then obtained the 3–5-year incidence rate by applying to the 0–2 year incidence rate the relative proportion of cases that were 3–5 year old in the IRSSN study. Cumulating the incidence risk in the 4 months to 2 years with that in the 3–5 years provided the 4 months to 5 years risk of rotavirus related events. The number needed to vaccinate (NNV), under assumptions of no indirect effect, is provided by the inverse of the product of vaccine efficacy and absolute risk in the unvaccinated. We assumed national immunization coverage to be 74% and no herd protection while projecting the events averted.

2.5. Healthcare costs due to rotavirus infection

The data for estimation of healthcare costs of rotavirus disease was obtained from two published studies [21,22], conducted in 2006 and 2009 respectively, that used the WHO generic protocol [23] to estimate the economic burden of diarrhea including direct medical and non-medical (e.g., travel costs to and from the hospital) costs through review of patient charts, healthcare facility records, pharmacy records, and patient family interviews.

Healthcare costs, both hospitalizations and outpatient visits, were divided into three levels – primary, secondary, and tertiary. Secondary and tertiary level outpatient visits were further divided

Table 1
Sources of diarrheal morbidity data in India and rotavirus specific disease rates.

Name of the study	Location/time	Sample size	Follow-up frequency	Rotavirus GE Rate per 1000 children			
				Hospitalizations	Out-patient visits	Episodes	Reference
Cryptosporidium transmission study	Vellore2008–2011	176	Weekly	12.8	47.8	121.2	[14,15]
Cryptosporidium immune response study	Vellore2009–2013	497	Biweekly	15.3	57.4	–	Unpublished
MAL-ED cohort study	Vellore2010–2014	251	Biweekly	10.7	40.1	217.5	Unpublished
Lactobody study	Vellore2011–2012	163	Weekly	13	48.8	292.5	Unpublished
Delhi cohort	Delhi 2009–2010	200	Weekly	16.1	60.2	160.6	[16]

into two categories – those that occur in ambulatory clinics and those that occur in emergency rooms. It was assumed that 15% of all outpatient visits for secondary and tertiary level care occurred via emergency visits and 85% occurred via ambulatory clinics. Also, the proportion of rotavirus-related visits to primary, secondary and tertiary levels of care were considered to be 33%, 41% and 26% respectively, based on a multi-country estimate of healthcare utilization patterns [24]. The healthcare costs were calculated by using weights by the proportion of population that sought each level of care and then multiplied by the total number of events. The total cost of rotavirus-related hospitalizations and outpatient visits in Indian children was calculated by multiplying the total number of yearly healthcare encounters attributable to rotavirus for children <5 years of age by the costs of each encounter, weighted for the proportion of population that sought each level of care.

All costs are reported in 2013 Indian rupees, adjusted for inflation. The Consumer *Price Index* (*CPI*) for India published by the World Bank was used for inflation-adjustment [25]. Total costs are also reported in U.S. dollars (1 USD = 60 INR).

Rotavac® was assumed to cost INR 50 per dose. It was also assumed that it would be administered within the current National Immunization Schedule and the incremental administrative cost per dose would not be more than INR 5 per dose. The total cost of vaccinating 1 child with 3 doses of Rotavac® is estimated at INR 165.

3. Results

3.1. Rotavirus related mortality

The 2011 UNICEF under-five mortality rate for India is 61 per 1000 live births. The MDS estimates the proportionate mortality due to diarrhea in <5 year children to be 13.2%. Thus the under-5 diarrheal mortality rate in India is 8.04 per 1000 live births or an annual mortality of 160.80 per 100,000 children. In the IRSSN, 1405 (39%) of 3580 children hospitalized with diarrhea during this period tested positive for rotavirus. Using WHO CHERG approach [20] of applying rotavirus proportion in hospitalized diarrhea to mortality data, the <5 rotavirus diarrhea mortality rate is 2.89/1000 live births or an annual rate of 58 per 100,000 children. Applying these rates of mortality to the 2011 birth cohort of India, estimated at 27,098,000 children, we estimate 78,583 deaths occur each year due to rotavirus with 59,336 of these deaths occurring in the first two years of life.

3.2. Rotavirus related morbidity

Based on the 2241 child years of follow up in five birth cohorts, with 108 diarrheal hospitalizations including 32 rotavirus diarrheal hospitalizations, the rotavirus hospitalization rate was 1427 per 100,000 children <2 years. The IRSSN data identified 88.2% of all <5 rotavirus diarrheal hospitalization occurs in children <2 years of age [12] providing a corrected estimate of 643 hospitalizations per 100,000 children <5 years age or 872,000 hospitalizations annually in India (Table 2).

Unpublished data from a large phase III clinical trial, where 1500 children in Vellore were followed up for the first two years life and healthcare provided for without cost to participants, provide a ratio of 3.75 rotavirus outpatient visits for every rotavirus hospitalization. The number of rotavirus diarrheal episodes requiring outpatient visit is thus estimated annually in India at 3,270,000.

The < 5 year rotavirus gastroenteritis rate in the four cohorts where rotavirus testing was performed was 8394 episodes per 100,000 children. Extrapolating this rate to India's < 5 population 11.37 million episodes of rotavirus diarrhea occur each year.

3.3. Impact of rotavirus vaccines

The vaccine efficacy (VE) of Rotavac® against severe hospitalized rotavirus gastroenteritis was 53.6% and that against rotavirus gastroenteritis of any severity was 34%. The 4 month to 5 year risk of rotavirus related death, hospitalization and outpatient visit were 251, 2714, and 9891 per 100,000 children. Introduction of Rotavac® in the National Immunization Program at current immunization coverage would result in 26,985 fewer deaths, 291,756 fewer hospitalizations and 686,277 fewer outpatient visits each year in India assuming no indirect effects for the vaccine (Table 3).

The NNV to prevent one rotavirus related death was 743 children, while vaccinating 69 children would prevent a rotavirus hospitalization. Similarly, for every 29 children vaccinated one rotavirus outpatient visit can be averted.

3.4. Healthcare costs

The median total direct cost (medical and non-medical) associated with rotavirus hospitalization was calculated at Rs. 8417 at a tertiary care hospital, Rs. 6969 at a secondary level hospital and Rs. 1897 at a primary care hospital. For an outpatient visit the median cost was Rs. 225. Weighting these costs by the estimated healthcare seeking patterns at each level, we estimate that hospitalization due to rotavirus diarrhea cost the country INR 4.9 billion (3.3 to 6.9 billion) annually. Additionally the country spends about INR 5.38 billion (3.6–7.6 billion) on outpatient visits. The total cost of the rotavirus immunization program for the 2011 India birth cohort of 27,098,000 children was calculated at Rs. 4.47 billion or USD 74.5 million, which is less than rotavirus associated hospitalization costs.

4. Discussion

Despite gains in child survival and increased availability of effective interventions such as ORS, zinc and access to healthcare,

Table 2
Rotavirus disease burden estimates for India.

Burden	Rotavirus mortality	Rotavirus hospitalization	Rotavirus outpatient visits	Rotavirus gastroenteritis episodes
Rate (per 100,000 children under-5)	58	643.8	2414.3	8394
(95% CI)	(56.1–59.9)	(440.3–908.9)	(1651.4–3408.3)	(7193–9738)
Number of annual events in India	78,583	872,315	3,271,187	11,373,098
(95% CI)	(76,019–81,206)	(596,662–1,231,452)	(2,237,486–4,617, 948)	(9,745,967–13,194,028)

Table 3
Estimated impact of rotavirus vaccine introduction in India based on current disease burden and immunization coverage.

Annual Impact	Rotavirus mortality	Rotavirus hospitalization	Rotavirus outpatient visits
Events averted with 74% coverage given current vaccine efficacy	26,985	291,756	686,277
(LCI–UCI)	(26,105–27,884)	(220,225–410,097)	(475,230–953,501)
Events averted with 100% coverage given current vaccine efficacy	36,466	394,265	927,401
(LCI–UCI)	(35,278–37,681)	(270,574–554,185)	(642,202–1,288,515)
Number needed to vaccinate to prevent one event	743	69	29

LCI–UCI, lower confidence interval–upper confidence interval.

rotavirus diarrhea continues to result in substantial mortality and morbidity for children in India and is a significant economic burden to the healthcare system and society. Each year in India, rotavirus causes an estimated 78,500 deaths, 872,000 hospitalizations, and over 3.2 million outpatient visits in children <5 years of age. In other words, by 5 years of age, 1 in every 334 – 356 Indian children will die from rotavirus diarrhea, 1 in every 22 – 45 children will be hospitalized, and 1 in every 6 – 12 children will have visited an outpatient clinic for rotavirus diarrhea (Fig. 1). Despite the lower vaccine efficacy of oral rotavirus vaccines in developing countries, because of the large disease burden these vaccines are predicted to alleviate substantial rotavirus mortality and morbidity [26]. Introduction of Rotavac® at current national coverage, will avert 27,000 deaths, 291,000 hospitalizations and 686,000 outpatient visits annually.

The national estimates of rotavirus deaths are slightly lower than rates previously estimated and are likely due to overall decline in diarrheal mortality. Rotavirus continues to contribute 39% of all diarrhea hospitalizations reiterating its position as the most important cause of diarrheal mortality. This reduction in mortality may reflect a greater impact of interventions to improve sanitation and hygiene on the burden of bacterial diarrhea, which is often transmitted through contaminated food and water, as opposed to rotavirus, which has multiple modes of transmission. The decline in child mortality in the past two decades may also be a function of better access to fluid replacement therapy and inpatient healthcare [3]. Our estimates of rotavirus hospitalizations are higher than previous estimates [9,19]. This may, in part, be a result of lower threshold for hospitalization in intensely followed up cohorts, but is also more likely to represent the true need for hospitalization where there is no constraint to accessing healthcare and contributes significantly to better survival. We therefore argue that our estimates of hospitalizations and outpatient care reflect more accurately the demand on health resources, as access constraints are removed through processes and structures established in research studies. Our estimate of rotavirus outpatient visits are lower than those estimated by Parashar and colleagues

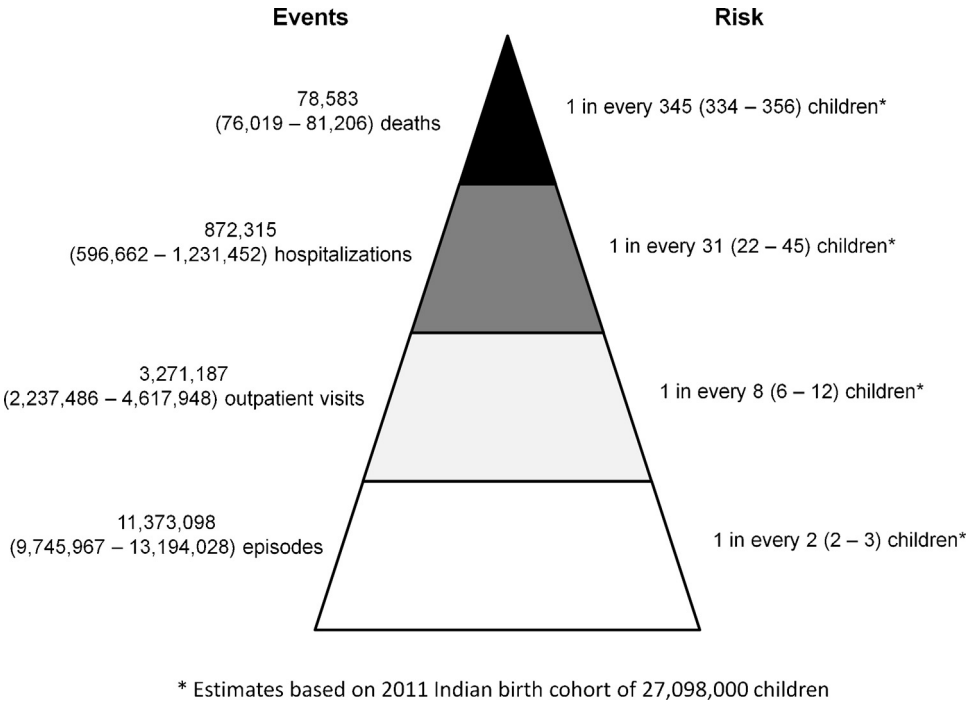

Fig. 1. Estimated annual number and risk of death, hospitalization, outpatient visits and diarrheal episodes due to rotavirus in children <5 years of age in India.

[8,9] because a conservative ratio of rotavirus outpatient visits to hospitalization obtained from a phase III rotavirus vaccine trial cohort of 1500 children observed for two years was used in which two-thirds of children had received a rotavirus vaccine. The ratio of outpatient rotavirus gastroenteritis visits to rotavirus gastroenteritis admission in the phase III clinical trial population was 3.75, and may have been lower because of the prompt administration of rehydration solutions at home decreasing mild or moderate disease, which points again to higher need for healthcare due to rotavirus disease than has previously been estimated. These are findings that must be considered as policy makers shift from impact estimation based on mortality alone to disease reduction.

This study has several limitations. First, four of the five cohorts that contributed to the estimation of rotavirus related morbidity were from a single site in Vellore. It is likely that morbidity rates and health-seeking characteristics of this population differs from higher mortality regions of India and limits the validity of extrapolations from these geographically limited cohorts. Nonetheless, given that health characteristics and health care access in Tamil Nadu are better than most other parts of India, it is likely that the estimates based on Tami Nadu are very conservative. Second, the <5 mortality rate is the number of <5 deaths per 1000 live births in a year and does not provide a direct estimate of probability of death between 0 and 5 years required for calculating deaths averted and NNV. Third, there is limited information on the rate of rotavirus morbidity in the 3–5 year age group. This analysis assumes a constant rate of events in the 4 months to 2 years age group and applies an adjusted estimate to the 3–5 year age group where no or limited direct estimates are available. Similarly we applied the ratio of outpatient to inpatient rotavirus gastroenteritis among the clinical trial participants to estimate the number of ambulatory rotavirus gastroenteritis visits. Despite there being no active referral to hospital for diarrheal episodes, free and better healthcare access in the clinical trial environment could have inflated the number of outpatient visits. This must be considered against the underestimation of the impact on society due to rotavirus disease that occurs when outpatient and hospitalization rates do not account for barriers in access to appropriate levels of healthcare. Furthermore, the increased access to ambulatory care might, by early diagnosis and treatment, prevent progression of disease to more severe presentation and thus contribute to lower estimates of mortality and hospitalization. Fourth, this analysis assumes that vaccine efficacy approximates effectiveness. Rotavirus disease burden is greatest in the first two years of life and timely immunization is necessary to achieve the anticipated effectiveness. Finally, the economic evaluation presented here is a comparison of direct costs while a full cost effectiveness analysis would inform policy more comprehensively.

In summary, rotavirus diarrhea continues to be the most important cause of diarrheal deaths, hospitalizations, and outpatient visits annually for children <5 years of age in India, and is a major economic burden. Despite the inherent challenges in developing national estimates of disease and economic burden for a large and diverse country like India, given the relative paucity of robust representative data, our estimates from these community-based cohorts provide the morbidity burden and the relative benefit of a rotavirus vaccine on both morbidity and mortality, which are not available from surveys or studies that have not assessed etiology. In addition to these estimates, further research into the cost effectiveness of the vaccine and the potential indirect effects of the vaccine would assist policy makers to decide on vaccine introduction in the national immunization program.

Conflicts of interest

None declared.

References

[1] UNICEF. Levels and Trends in Child Mortality Report. New York; 2012.
[2] Walker CLF, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. Global burden of childhood pneumonia and diarrhoea. Lancet 2013;381:1405–16.
[3] Bhutta ZA, Das JK, Walker N, Rizvi A, Campbell H, Rudan I, et al. Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? Lancet 2013;381:1417–29.
[4] Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet 2010;375:1969–87.
[5] Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012;379:2151–61.
[6] Lahariya C, Paul VK. Burden, differentials, and causes of child deaths in India. Indian J Pediatr 2010;77:1312–21.
[7] Kotloff KL, Nataro JP, Blackwelder WC, Nasrin D, Farag TH, Panchalingam S, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case–control study. Lancet 2013;382:209–22.
[8] Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. Emerg Infect Dis 2006;12:304–6.
[9] Tate JE, Chitambar S, Esposito DH, Sarkar R, Gladstone B, Ramani S, et al. Disease and economic burden of rotavirus diarrhoea in India. Vaccine 2009;27(Suppl. 5):F18–24.
[10] Morris SK, Awasthi S, Khera A, Bassani DG, Kang G, Parashar UD, et al. Rotavirus mortality in India: estimates based on a nationally representative survey of diarrhoeal deaths. Bull World Health Organ 2012;90:720–7.
[11] Srivastava NM, Awasthi S, Agarwal GG. Care-seeking behavior and out-of-pocket expenditure for sick newborns among urban poor in Lucknow, northern India: a prospective follow-up study. BMC Health Serv Res 2009;9:61.
[12] Kang G, Arora R, Chitambar SD, Deshpande J, Gupte MD, Kulkarni M, et al. Multicenter, hospital-based surveillance of rotavirus disease and strains among Indian children aged <5 years. J Infect Dis 2009;200(Suppl. 1):S147–53.
[13] Million Death Study C, Bassani DG, Kumar R, Awasthi S, Morris SK, Paul VK, et al. Causes of neonatal and child mortality in India: a nationally representative mortality survey. Lancet 2010;376:1853–60.
[14] Sarkar R, Ajjampur SS, Prabakaran AD, Prabakaran AD, Geetha JC, Geetha JC, et al. Cryptosporidiosis among children in an endemic semiurban community in southern India: does a protected drinking water source decrease infection? Clin Infect Dis 2013;57:398–406.
[15] Sarkar R, Sivarathinaswamy P, Thangaraj B, Sindhu KN, Ajjampur SS, Muliyil J, et al. Burden of childhood diseases and malnutrition in a semi-urban slum in southern India. BMC Public Health 2013;13:87.
[16] Chandola TR, Taneja S, Goyal N, Rathore SS, Appaiahgari MB, Mishra A, et al. Descriptive epidemiology of rotavirus infection in a community in North India. Epidemiol Infect 2013;141:2094–100.
[17] Rothman KJ, Boice JD. Branch NCIEE, Health NIo, Epidemiology HUDo. Epidemiologic analysis with a programmable calculator. Dept. of Health, Education, and Welfare, Public Health Service, National Institutes of Health; 1979.
[18] World Health Statistics Report. Geneva: World Health Organization; 2013.
[19] Munos MK, Walker CL, Black RE. The effect of rotavirus vaccine on diarrhoea mortality. Int J Epidemiol 2010;39(Suppl. 1):i56–62.
[20] Walker N, Fischer-Walker C, Bryce J, Bahl R, Cousens S. Effects CRGoI. Standards for CHERG reviews of intervention effects on child survival. Int J Epidemiol 2010;39(Suppl. 1):i21–31.
[21] Sowmyanarayanan TV, Patel T, Sarkar R, Broor S, Chitambar SD, Krishnan T, et al. Direct costs of hospitalization for rotavirus gastroenteritis in different health facilities in India. Indian J Med Res 2012;136:68–73.
[22] Mendelsohn AS, Asirvatham JR, Mkaya Mwamburi D, Sowmynarayanan TV, Malik V, Muliyil J, et al. Estimates of the economic burden of rotavirus-associated and all-cause diarrhoea in Vellore, India. Trop Med Int Health 2008;13:934–42.
[23] WHO. Generic Protocol for Rotavirus Burden Estimation. Geneva: WHO; 2002.
[24] Adam T, Evans DB, Murray CJ. Econometric estimation of country-specific hospital costs. Cost Eff Resour Alloc 2003;1:3.
[25] Consumer Price Index. The World Bank Group; 2014. Accessed at: http://data.worldbank.org/indicator/FP.CPI.TOTL [06.01.14].
[26] Babji S, Kang G. Rotavirus vaccination in developing countries. Curr Opin Virol 2012;2:443–8.