

Original Papers

A Prospective Hospital-based Surveillance to Estimate Rotavirus Disease Burden in Bhutanese Children under 5 Years of Age

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Abstract: As part of efforts to develop an informed policy for rotavirus vaccination, this prospective study was conducted to estimate the burden of rotavirus diarrhea among children less than 5 years old attended to the Department of Pediatrics, Jigme Dorji Wangchuk National Referral Hospital (JDWNRH), Thimphu, Bhutan. The duration of the study was three years, extending from February 2010 through December 2012. We estimated the frequency of hospitalization in the pediatric ward and dehydration treatment unit (DTU) for diarrhea and the number of events attributable to rotavirus infection among children under 5 years of age. During the study period, a total of 284 children (1 in 45) were hospitalized in the pediatric ward, and 2,220 (1 in 6) in the DTU with diarrhea among children residing in the Thimphu district. Group A rotavirus was detected in 32.5% and 18.8% of the stool samples from children hospitalized in the pediatric ward, respectively. Overall, 22.3% of the stool samples were rotavirus-positive, and the majority (90.8%) of them was detected in children under 2 years of age. From this study, we estimated that the annual incidence of hospitalization in the pediatric ward and DTU due to rotavirus diarrhea was 2.4/1000 (95% CI 1.7–3.4) and 10.8/1000 (95% CI 9.1–12.7) children, respectively. This study revealed that rotavirus is a major cause of diarrhea in Bhutanese children in Thimphu district and since no study has been performed previously, represents an important finding for policy discussions regarding the adoption of a rotavirus vaccine in Bhutan.

Key words: Rotavirus, Burden, Vaccine, Children, Bhutan

INTRODUCTION

Rotaviruses infect almost every child by the age of 3 to 5 years and constitute the leading cause of acute diarrhea in children under 5 years of age [1]. According to the World Health Organization (WHO), 453,000 (95% CI 420,000–494,000) children die annually from rotavirus infection. Five countries (India, Nigeria, the Democratic Republic of the Congo, Ethiopia and Pakistan) accounted for more than half of all rotavirus deaths in children under 5 years of age [2].

Based on the presence of specific antigens, rotaviruses are classified into seven groups (A–G) of which only A, B, and C infect humans. Group A rotavirus is the most common, and its genotypes G1, G2, G3, G4, G9, P[4] and

P[8] cause the majority of human infections [3]. Although rotavirus vaccine is commercially available to prevent severe rotavirus infection, it has not been introduced in the national immunization program of Bhutan because many policy makers and health care providers do not recognize the burden of rotavirus infection.

Bhutan is a lower middle income country in South Asia with modest access to health care, even in the most remote and difficult geographical terrain. The country has made many strides in lifting its socio-economic status, and, as a result, the poverty level has been reduced from 31% in 2003 to 12% in 2012. Life expectancy has increased from 66 years in 1999 to 68 years in 2012, and the population growth rate has stabilized to around 1.3% from 3.1% in 1994 [4]. There has also been a significant reduction in in-

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fant mortality rate (30/1000 live birth) under 5 mortality rate (37.3%), and Bhutan is on track to achieve most of the MDG targets by 2015. With “Gross National Happiness” at the pinnacle of its developmental philosophy, Bhutan is striving to achieve economic self-reliance and full employment (97.5%) by 2020.

The current population of the country is approximately 706,800, and children under 5 years of age comprise approximately 10% of the total population with an annual birth cohort of 14,000 [5]. Diarrhea continues to be one of the major causes of morbidity among this group of children despite good coverage of safe drinking water and sanitation in the country [4]. Although vaccines are available for rotavirus, no study has been conducted so far to determine the burden of diarrhea in Bhutan. This study, therefore, aims to estimate the burden of rotavirus diarrhea among children under 5 years of age presenting with acute diarrhea at the Jigme Dorji Wangchuk National Referral Hospital (JDWNRH) and in that way to generate evidence that will contribute to policy discussions by the Ministry of Health on its diarrheal disease control program and the introduction of rotavirus vaccination in the country. Currently, rotavirus vaccine is neither part of the routine immunization program nor available in the private market.

The foremost national referral hospital in the country, JDWNRH is situated in the capital city (Thimphu) of the Thimphu district and primarily serves the population of the Thimphu city and district.

METHODS

Following the WHO Generic Protocol for the surveillance of rotavirus infection [6], the study was carried out in the Department of Pediatrics, JDWNRH for a period of three years from January 2010 through December 2012. Any child under 5 years of age with acute diarrhea either admitted to the pediatric ward or hospitalized in the DTU for dehydration treatment was enrolled in this study. DTU is a pediatric clinic unit where acute diarrhea cases receive rehydration and supportive treatment without staying overnight. Children can be treated with intravenous fluid in the DTU, but severe cases are referred to pediatric ward for hospitalization.

In this study, acute diarrhea was defined as the passing of three or more loose stools within the preceding 24 hours starting no more than 72 hours before presentation. Basic demographic data for each enrolled case was recorded by the nurses and laboratory officers involved in the study. Informed consent was obtained from the parents of all the enrolled children and the study was approved by the Research Ethics Board of Health, Bhutan.

The stool samples were collected into a labeled, sterile, dry container and transported on ice to the Public Health Laboratory (PHL) for testing. The PHL is the national referral laboratory functioning under the Ministry of Health and situated in Thimphu city, adjacent to the JDWNRH premises. The stool samples were stored at -80°C until testing for the presence of rotavirus antigens (period of stool storage varied from 14–30 days). The Rotaclone enzyme immunoassay (EIA) kit (Meridian Diagnostics, Inc. Cincinnati, OH, USA) and Ridascreen rotavirus EIA kit (R-Biopharm, Darmstadt, Germany) were used for the detection of group A rotavirus antigens in the stool samples according to the manufacturers’ instructions. Each plate included a negative and a positive control.

To estimate the burden and proportion of diarrhea caused by rotavirus, the average number of diarrhea cases in both the pediatric ward and DTU in 2010, 2011, and 2012 was extrapolated by the positivity rate for rotavirus detected among hospitalized cases in the same period [7]. Thimphu district has two more hospitals and 10 primary health centers, but most of the children would seek medical care in JDWNRH since 85% of children under 5 years in the Thimphu district reside in Thimphu city as per the National Statistics Bureau population project [4]. Therefore, the denominator of children under 5 years was taken from the Thimphu district for burden estimation. The rates and the 5-years cumulative risk of rotavirus diarrhea were determined using the population of children under 5 years of age in Thimphu district ($n = 12,912$), projected by the National Statistics Bureau, Royal Government of Bhutan [5].

RESULTS

Diarrhea-associated hospitalization in the pediatric ward and DTU

During the three-year study period, a total of 4,137 (1,400 in 2010, 1,468 in 2011, and 1,269 in 2012) children under 5 years of age were hospitalized in the pediatric ward at JDWNRH, or an annual average of 1,379 (95% CI 1,208.5–1,549.5). Among them, 284 (6.9%) were hospitalized due to acute diarrhea (90 in 2010, 98 in 2011, and 96 in 2012) or an annual average of 95 (95% CI 87.6–101.7). In the same period, a total of 2,220 children with acute diarrhea treated in the DTU (879 in 2010, 667 in 2011, and 674 in 2012) or an annual average of 740 (95% CI 536.9–943.0). Therefore, a total of 39% of children ($95 + 740/2119$) were hospitalized with diarrhea in this study. For children hospitalized in the ward and DTU, the mean age was 16.3 (95% CI 14.6–18.0) and 13.4 months (95% CI 12.9–13.9), respectively. Among the total cases of diar-

rhea, the male: female ratio was 1:0.8 (the proportion of hospitalized in males and females was 54.9% and 45.0%, respectively, and the proportion of DTU males and females was 55.9% and 46.0%, respectively).

Proportion of rotavirus-positive stool samples

The proportion of stools positive for rotavirus diarrhea in Bhutanese children was 22.3% (139/624) (95% CI 19.2–25.7). Among the children hospitalized in the ward and DTU, 32.5 (51/157) (95% CI 25.6–40.1) and 18.8% (88/467) (95% CI 15.5–22.6) were positive for rotavirus, respectively. The frequency was higher in patients hospitalized in the ward than in DTU patients. Rotavirus was predominant (90.8%) in children under 2 years of age. The highest frequency of rotavirus diarrhea occurred in children aged 6–11 months (41.2%), followed by children aged 12–23 months (29.4%). Rotavirus was also detected in children aged 3–5 months (15.9%) and infants aged 0–2 months (4.2%). The lowest prevalence was observed in children aged 24–59 months (Fig. 1). In the 24–35, 36–47, and 48–59 month age groups, rotavirus was detected in 7.6, 1.7, and 0% of the samples, respectively.

Seasonality

The rotavirus infection rate was higher during the winter-spring season (December–April), mainly in January, February and March. Although cases were detected in other months, no case was detected in September, October

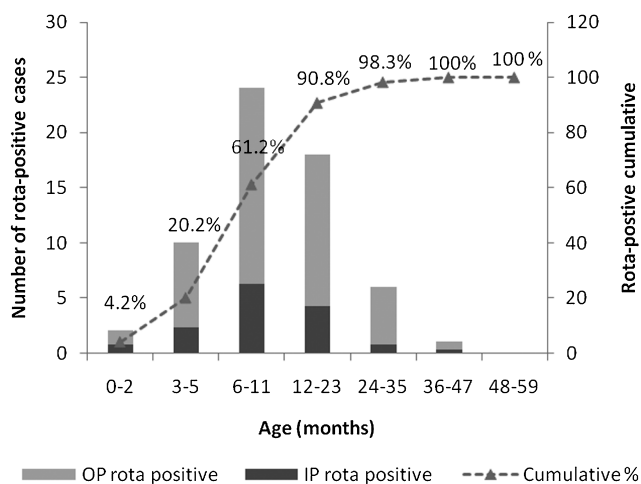


Fig. 1 The distribution of rotavirus diarrhea cases in Bhutanese children under 5 years of age. The columns represent the number of patients among the indicated age categories. Grey and black indicate the number of admitted and outpatients, respectively. The line shows the cumulative percentage of rotavirus-positive children by age. By the age of 36–47 months 100% of the Bhutanese children are infected rotavirus.

or November. A seasonality trend was also observed in all diarrheal cases, including patients hospitalized in both the ward and the DTU where one peak occurred in the winter and another in the summer (Fig. 2).

Estimates of rotavirus diarrhea burden

Based on the annual average number of hospitalized diarrhea cases in the ward and DTU and the number of laboratory-confirmed rotavirus infections, we estimated that the annual incidence of hospitalization due to rotavirus diarrhea was 2.4/1000 (95% CI 1.7–3.4) in the ward and 10.8/1000 (95% CI 9.1–12.7) in the DTU. The cumulative 5-year risk for rotavirus diarrhea-associated hospitalization in the ward and DTU was estimated to be 1 in 416 and 1 in 93 children, respectively (Table 1).

DISCUSSION

This study represents the first estimation of rotavirus diarrhea burden in Thimphu as part of efforts to elucidate the burden of rotavirus diarrhea among diarrheal cases in Bhutanese children under 5 years old. We determined that one-third of the children hospitalized with diarrhea were infected by rotavirus. This is substantially higher than the median proportion of diarrhea hospitalizations estimated for developing countries (21%) [8], China (27.9%) [9], and Turkey (20%) [10]. However, these results are comparable to those found in hospital-based studies conducted in countries such as India (35.4%) [11], England (34%) [12], and the USA (> 30%) [13]. The overall prevalence of rotavirus

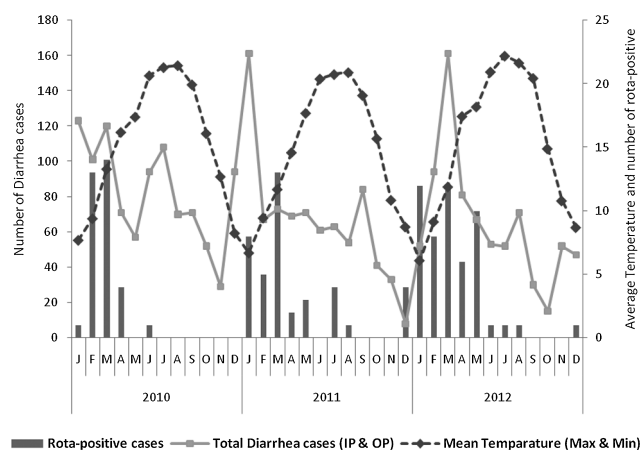


Fig. 2 Monthly occurrence of rotavirus diarrheal cases in Bhutanese children. The columns represent the number of total rotavirus-positive cases. The grey line indicates the total number of children with diarrhea. The black line indicates the average monthly temperature of Thimphu.

Table 1 Burden of rotavirus diarrhea among Bhutanese children < 5 years.

Burden	Average annual estimates for 2010–2012				Cumulative 5-year risk for rotavirus diarrhea
	Diarrhea related	Rotavirus-positive (%)	Rotavirus related	Rotavirus related diarrhea/1000 children	
Hospitalization	95	32.5	31	2.4	1 in 416
Outpatient clinic visits	740	18.8	139	11	1 in 93

was similar to that reported from other South Asian countries, such as Sri Lanka (21.9%) [14] and India [15]. However, the prevalence was higher than that observed in Nepal (17%) [16] and Hong Kong (12%) [17] and lower than that in Bangladesh (39.5%) [18].

The age distribution of diarrhea-related hospitalization in the ward and DTU was consistent with the worldwide epidemiological profile of diarrhea, where the highest number of hospitalizations occurs during the first 2 years of life and males show a higher hospitalization rate than females [7]. The peak of rotavirus infection in Bhutanese children occurred at a young age, which is consistent with results found in other developing countries such as Bangladesh [18], but not in Turkey [19] or Sri Lanka [20]. By the age of 36–47 months, 100% of Bhutanese children have been infected with rotavirus, which is earlier than in other countries [16]. It has been observed that the rate of rotavirus infection decreases with increasing age due to the acquired immunity that comes with symptomatic and/or asymptomatic infection [21–23]. It is possible, therefore, that Bhutanese children are repeatedly exposed or infected with rotaviruses earlier than children in other parts of the world.

Rotavirus infection is generally seasonal in countries with a temperate climate but it can occur year round [19]. The distinctly different seasonal patterns of rotavirus infection in countries with similar geographical locations, climates and levels of development indicate that a single unifying explanation for variation in the seasonality of rotavirus infection is unlikely [24]. Understanding the seasonal patterns of rotavirus has several implications, such as testing the efficacy of currently available vaccines and the vaccine implementation programs [25]. We found that rotavirus infection in Bhutan is predominantly seasonal, occurring in the winter-spring season, similar to the findings from countries in temperate climates [17, 26, 27]. Bhutan has different geographical regions, but as a whole, there are four seasons. Spring starts in early March and lasts until mid-April, which is windy and relatively dry. Summer commences in mid-April with occasional showers, and it continues with the monsoon season from late June through late September with heavy rainfall. Autumn commences from late September to late November and is characterized

by bright, sunny days and some early snowfall at higher elevations. From late November until February, winter sets in with frost throughout much of the country, and snowfall is common at elevations above 3,000 meters. Hills surrounding the Thimphu valley rise to an altitude of 2,000–3,800 meters, and the city itself has an altitude ranging from 2,248–2,648 meters, which is within the warm temperate zone (2,000–3,000 meters). The average temperature during winter varies between –2.6 and 14.5 C and in the summer between 15 and 25.9 C [28, 29].

The severity of illness and higher prevalence in infants, but not socioeconomic conditions, are associated with rotavirus seasonality [30]. The seasonal pattern observed in rotavirus may be influenced by several factors such as environmental conditions, social behaviors, health practices, socio-demographic factors, birth rate and circulating strain types [25]. We observed two peaks in the occurrence of diarrheal cases, one in the cold season and the other during the hot season. According to our experience, the peak in the hot season is caused by enteric bacteria. The current study provided evidence that the peak in the cold season is largely caused by rotavirus and possibly other enteric viruses that are currently unknown. We can designate December to April as the rotavirus season in Bhutan.

The annual incidence of hospitalization in the pediatric ward and DTU due to rotavirus diarrhea in Bhutanese children was similar to the rates of hospitalization in the ward (2.1–5.5/1000 children per year) and DTU (12.1–43.9/1000 children per year) reported from other developing countries [31]. Notably, these findings are very similar to the estimates (2.8 and 12.1/1000 children per year) from the Philippines where the prevalence of rotavirus diarrhea in hospitalized children (31%) was similar to that in Bhutan [32]. Our estimation of the cumulative 5-year risk for rotavirus diarrhea-associated hospitalizations was low compared with that found in other countries [7]; however, we could not compare Bhutan with countries in this region due to the lack of published data. We found only one death due to diarrhea in this study, and a sample was not collected. Therefore the etiology of that case is unknown. Compared with 1990, the deaths from diarrheal diseases in children decreased from 2.5 to 1.4 million by 2010 [33]. At

a cost of \$0.30 per treatment, the combination of oral rehydration solution and zinc reduces the risk of death in children with acute diarrhea to close to zero [34]. We believe that introducing this treatment nationwide has significantly reduced the mortality due to diarrhea among Bhutanese children. However, it is important to remember that patients from remote areas with severe diarrhea may expire before arriving at the hospital and that these cases remain undocumented.

This study represents the first sentinel hospital surveillance following the WHO generic protocol to estimate the rotavirus burden in Bhutan. Because of the restriction on hospitalization for diarrheal cases due to the limited number of beds in the pediatric ward, this study represents only very severe cases. An additional limitation of this type of study in developing countries is that the burden of rotavirus diarrhea tends to be underestimated because many children who have illness of mild severity and who could potentially be rotavirus-positive are not brought in for medical treatment by their parents [7]. The present surveillance study had several limitations. First, there was suboptimal documentation of the acute diarrhea cases, both in the pediatric ward and the DTU. Second, the enrollment of the children was dependent on the guardians' desire to participate in the study. Third, the collection of stool samples and clinical information from the enrolled children with acute diarrhea from the ward and DTU was difficult because few had participated in this type of study before. Fourth, we had to use the population of children under 5 years old in the Thimphu district as a denominator to estimate the rotavirus disease burden, but children from other districts might have also visited the JDWNRH because it is a national referral hospital in Bhutan. Nevertheless, the number of such cases was probably too small to influence the outcome of this study because most of the district hospitals are capable of treating severe diarrhea cases. Therefore, efforts should be made to ensure that health care personnel understand the importance of documentation and research. There are no private practitioners in Bhutan, and every citizen is treated free of charge. JDWNRH has a large number of patients in proportion to the number of health care personnel; therefore, priority is placed on saving lives and curing the patients. However, it is also important to note that the data generated by this type of study provide important public health information and can reduce the disease burden and consequently decrease the admission of patients to hospitals.

Despite the limitations, the present study revealed that rotavirus is one of the major causes of morbidity among children under 5 years of age in Bhutan, a finding similar to that in other countries in the region. However, unlike

those countries and other developing countries, mortality due to diarrhea or rotavirus is very rare among hospitalized children.

This study provided insights and baseline information on the rotavirus disease burden in children under 5 years of age in a national referral hospital. We hope that the experience gained and the results generated in the present study provide a model that could be adopted to study the national rotavirus disease burden, thereby enabling policymakers to make informed decisions regarding diarrheal disease control, especially with regard to the introduction of the rotavirus vaccine in Bhutan.

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REFERENCES

1. WHO. Rotavirus. WHO position paper—January 2013. *Wkly Epidemio/Rec* 2013; 88: 49–64.
2. WHO. 2012. Estimated rotavirus deaths for children under 5 years of age: 2008, 453000. Available: http://www.who.int/immunization/monitoring_surveillance/burden/estimates/rotavirus/en/
3. Houry H, Ogilvie I, El Khoury AC, et al. Burden of rotavirus gastroenteritis in the Middle Eastern and North African pediatric population. *BMC Infect Dis* 2011; 11: 9.
4. Ministry of Health, Royal Government of Bhutan. Annual Health Bulletin 2012. In., 25 edn. Thimphu: Bhutan Health Information Management System 2013.
5. National Statistics Bureau, Royal Government of Bhutan. Dzongkhag population projections 2006–2015. 2008: 1–203.
6. Bresee J, Parashar U, Holman R, et al. Part I: Generic protocol for hospital-based surveillance to estimate the burden of rotavirus gastroenteritis in children under 5 years of age. Geneva: World Health Organization; 2002: 1–77.
7. Hsu VP, Abdul Rahman HB, Wong SL, et al. Estimates of the burden of rotavirus disease in Malaysia. *J Infect Dis* 2005; 192 Suppl 1: S80–86.
8. Parashar UD, Hummelman EG, Bresee JS, et al. Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis* 2003; 9: 565–572.
9. Ouyang Y, Ma H, Jin M, et al. Etiology and epidemiology of viral diarrhea in children under the age of five hospitalized in Tianjin, China. *Arch Virol* 2012; 157: 881–887.
10. Hacimustafaoglu M, Celebi S, Agin M, et al. Rotavirus epidemiology of children in Bursa, Turkey: a multi-centered hospital-based descriptive study. *Turk J Ped* 2011; 53: 604–613.

11. Sowmyanarayanan TV, Ramani S, Sarkar R, et al. Severity of rotavirus gastroenteritis in Indian children requiring hospitalization. *Vaccine* 2012; 30 Suppl 1: A167–172.
12. Ryan MJ, Ramsay M, Brown D, et al. Hospital admissions attributable to rotavirus infection in England and Wales. *J Infect Dis* 1996; 174 Suppl 1: S12–18.
13. Chang HG, Glass RI, Smith PF, et al. Disease burden and risk factors for hospitalizations associated with rotavirus infection among children in New York State, 1989 through 2000. *Ped Infect Disease J* 2003; 22: 808–814.
14. Ahmed K, Batuwanthudawe R, Chandrasena TG, et al. Rotavirus infections with multiple emerging genotypes in Sri Lanka. *Arch Virol* 2010; 155: 71–75.
15. Kang G, Kelkar SD, Chitambar SD, et al. Epidemiological profile of rotaviral infection in India: challenges for the 21st century. *J Infect Dis* 2005; 192 Suppl 1: S120–126.
16. Uchida R, Pandey BD, Sherchand JB, et al. Molecular epidemiology of rotavirus diarrhea among children and adults in Nepal: detection of G12 strains with P[6] or P[8] and a G11P[25] strain. *J Clin Microbiol* 2006; 44: 3499–3505.
17. Mitui MT, Chan PK, Nelson EA, et al. Co-dominance of G1 and emerging G3 rotaviruses in Hong Kong: a three-year surveillance in three major hospitals. *J Clin Virol* 2011; 50: 325–333.
18. Ahmed K, Ahmed S, Mitui MT, et al. Molecular characterization of VP7 gene of human rotaviruses from Bangladesh. *Virus Genes* 2010; 40: 347–356.
19. Bozdayi G, Dogan B, Dalgic B, et al. Diversity of human rotavirus G9 among children in Turkey. *J Med Virol* 2008; 80: 733–740.
20. Chandrasena N, Rajindrajith S, Ahmed K, et al. Hospital-based study of the severity and economic burden associated with rotavirus diarrhea in Sri Lanka. *J Ped Infect Dis* 2009; 4: 379–386.
21. Ndze VN, Akum AE, Kamga GH, et al. Epidemiology of rotavirus diarrhea in children under 5 years in Northern Cameroon. *Pan African Med J* 2012; 11: 73.
22. Odimayo MS, Olanrewaju WI, Omilabu SA, et al. Prevalence of rotavirus-induced diarrhea among children under 5 years in Ilorin, Nigeria. *J Trop Ped* 2008; 54: 343–346.
23. Jiang B, Gentsch JR, Glass RI. The role of serum antibodies in the protection against rotavirus disease: an overview. *Clin Infect Dis* 2002; 34: 1351–1361.
24. Patel MM, Pitzer V, Alonso WJ, et al. Global Seasonality of Rotavirus Disease. *Ped Infect Dis J* 2013; 32: e134–e147.
25. Jagai JS, Sarkar R, Castronovo D, et al. Seasonality of rotavirus in South Asia: a meta-analysis approach assessing associations with temperature, precipitation, and vegetation index. *PLoS One* 2012; 7: e38168.
26. Diggle L. Rotavirus diarrhoea and future prospects for prevention. *Br J Nurs* 2007; 16: 970–974.
27. Gleizes O, Desselberger U, Tatochenko V, et al. Nosocomial rotavirus infection in European countries: a review of the epidemiology, severity and economic burden of hospital-acquired rotavirus disease. *Ped Infect Dis J* 2006; 25(1 Suppl): S12–21.
28. Anonymous: Thimphu City, State of the Environment. In. Thimphu: Ministry of Works and Human Settlement, Royal Government of Bhutan; 2007: 71.
29. Bhutan, Official Website of the Tourism Council of Bhutan. Available: <http://www.tourism.gov.bt>
30. Schael IP, Gonzalez R, Salinas B. Severity and age of rotavirus diarrhea, but not socioeconomic conditions, are associated with rotavirus seasonality in Venezuela. *J Med Virol* 2009; 81: 562–567.
31. Kawai K, O'Brien MA, Goveia MG, et al. Burden of rotavirus gastroenteritis and distribution of rotavirus strains in Asia: a systematic review. *Vaccine* 2012; 30: 1244–1254.
32. Carlos CC, Inobaya MT, Bresee JS, et al. The burden of hospitalizations and clinic visits for rotavirus disease in children aged <5 years in the Philippines. *J Infect Dis* 2009; 200 Suppl 1: S174–181.
33. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2095–2128.
34. Ralston ME, Day LT, Slusher TM, et al. Global paediatric advanced life support: improving child survival in limited-resource settings. *Lancet* 2013; 381: 256–265.