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Global Seasonality of Rotavirus Disease

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Abstract

Background—A substantial number of surveillance studies have documented rotavirus prevalence among children admitted for dehydrating diarrhea. We sought to establish global seasonal patterns of rotavirus disease before widespread vaccine introduction.

Methods—We reviewed studies of rotavirus detection in children with diarrhea published since 1995. We assessed potential relationships between seasonal prevalence and locality by plotting the average monthly proportion of diarrhea cases positive for rotavirus according to geography, country development, and latitude. We used linear regression to identify variables that were potentially associated with the seasonal intensity of rotavirus.

Results—Among a total of 99 studies representing all six geographical regions of the world, patterns of year-round disease were more evident in low- and low-middle income countries compared with upper-middle and high income countries where disease was more likely to be seasonal. The level of country development was a stronger predictor of strength of seasonality (P=0.001) than geographical location or climate. However, the observation of distinctly different seasonal patterns of rotavirus disease in some countries with similar geographical location, climate

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Contributors

MP, UP, VP, and CV created and designed the study. MP and DV collected the data. MP, JT, WA analyzed the data. MP, VP, WA, DV, JT, BL, CV, and UP interpreted the data. MP drafted the report. MP, VP, WA, DV, JT, BL, CV, and UP critically revised the report.

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and level of development indicate that a single unifying explanation for variation in seasonality of rotavirus disease is unlikely.

Conclusion—While no unifying explanation emerged for varying rotavirus seasonality globally, the country income level was somewhat more predictive of the likelihood of having seasonal disease than other factors. Future evaluation of the effect of rotavirus vaccination on seasonal patterns of disease in different settings may help understand factors that drive the global seasonality of rotavirus disease.

Keywords

rotavirus; seasonality; season; diarrhea; global; surveillance

Background

Rotavirus infection is the most common cause of severe diarrhea among children under 5 years of age in both developing and developed regions of the world.(1, 2) Seasonality of rotavirus infection has been shown to differ widely across the world. Several previous studies have undertaken efforts to improve understanding of factors favoring the variation in occurrence of rotavirus disease by season and locality. In a review of 34 studies conducted prior to 1990, Cook et al. found that rotavirus infection typically occurred during the winter months of the year in temperate regions, while year-round patterns were common in the warmer tropical regions.(3) Attempts to find a link between seasonal incidence of rotavirus disease and many aspects of climate, such as temperature, relative humidity, rainfall, and barometric pressure have yielded conflicting findings.(4–8)

The difficulty in finding an association between rotavirus disease and climatic, geographic, economic, or behavioral factors is related to the fact that most human activity and condition is intricately linked with or affected by climate. Another challenging aspect of findings explanations for rotavirus seasonality has been that, until recently, studies examining rotavirus prevalence have been limited in number from many regions of the world, and widely variable in terms of study design, use of laboratory assays, and reporting of data.(9) To address these concerns and better assess the burden of rotavirus disease in anticipation of vaccine introduction, in 2001, the World Health Organization (WHO) developed a generic protocol for conducting sentinel hospital-based rotavirus surveillance using standardized site selection procedures, surveillance design, enzyme immunoassays for rotavirus detection, and reporting parameters.(10) Simultaneously, funding from international donors has enabled the development of global epidemiology and laboratory networks of rotavirus surveillance. As a result of these two concerted efforts, an abundance of studies have been published in recent years, which have applied uniform procedures to examine the burden and seasonality of rotavirus disease.(1, 11)

We used the wealth of information that has recently become available to review the global prevalence of rotavirus disease before the widespread use of recently available rotavirus vaccines.(12) In addition, we reexamined the influence of localities on the seasonality of rotavirus disease on a global scale. We found that the recently published studies were broadly in agreement with previous observations that rotavirus disease tends to have a more strongly seasonal occurrence in temperate climates compared to tropical climates, where disease tends to occur year-round. However, we found that income level, rather than latitude or geographic region, was the strongest predictor of seasonality. Disentangling the effect of climate from other ecological factors such as income level, access to clean water, level of sanitation, birth rates, and interactions with animals (which could serve as proxies for the overall transmission rate) has been proven to be difficult, but could perhaps be better understood as these surveillance data accumulate.

METHODS

Search strategy and selection criteria

We reviewed all epidemiological studies published between January 1995 and December 2010 that assessed the prevalence of rotavirus among children with diarrhea. We searched PubMed MEDLINE using the following keywords: "rotavirus and season", and "rotavirus and seasonality." We did not limit our search by language. We limited our analysis to studies that met the following criteria: conducted in full-year increments; tested at least 50 children with acute gastroenteritis for rotavirus, using an enzyme immunoassay, polyacrylamide gel electrophoresis, or reverse-transcriptase polymerase chain reaction; provided monthly data on the proportion of all patients with diarrhea caused by rotavirus. We included studies from both inpatient and outpatient settings because seasonality is not expected to vary by treatment setting. If studies reported data from more than one city, we considered results from each city as a separate data point. We restricted our analysis to studies published since 1995 because studies prior to this date have previously been reviewed(3) and because, since the mid-1990s, most studies have employed sensitive and specific enzyme immunoassays when conducting surveillance for rotavirus, typically using the standardized surveillance methods recommended by the WHO. Eligible studies were selected and abstracted by a single author (DV) and reviewed by another author (MP). For each study that satisfied our criteria, we recorded the study city, country, duration, age of enrollees, proportion of rotavirus positive results by month, and the number of specimens tested and number of positive results if available.

Most studies provided proportion of diarrhea events positive for rotavirus, rather than the absolute numbers of rotavirus-positive tests. Among the few studies that presented both, the seasonal pattern of rotavirus infection was similar (data not shown). For studies longer than 12 months in duration, we averaged the proportion of diarrhea events positive for rotavirus during each month.

Data analysis

Previous studies have determined that seasonality of rotavirus disease may vary by region. To assess potential relationships between seasonal prevalence and locality, we plotted the average monthly proportion of diarrhea cases positive for rotavirus according to three inter-related groups: geographical area, level of country development, and latitude. First, we grouped studies according to six geographic regions of the world: North & Central America, South America, Asia, Africa, Europe, and Oceania. Second, we grouped studies according to the World Bank income stratification for the country represented by each study: low and low-middle income; high-middle income; and high-income countries. By summing monthly prevalence data across regions with rotavirus detection during opposing seasons could be misinterpreted as "year-round" disease. Thus, the grouping of studies by income level was restricted to the Northern Hemisphere and the tropical belt (i.e., latitudes 10° North and 10° South of the equator), where peak prevalence of disease was between December and May, and ignored countries in the Southern Hemisphere where peak prevalence of rotavirus disease occurred during May–October. Third, we grouped studies according to latitudes with broadly similar seasons: 36–70° North, 11–35° North, 10° North–10° South, 11°–35° South, and 36°–55° South. To account for the undue influence of studies with a smaller sample, the pooled averages for these groups were weighted according to study size.

We were also interested in determining predictors at the ecological level for apparent differences in the strength of seasonality of rotavirus disease on a global scale. To characterize seasonal variability in rotavirus disease, we used an indicator of "seasonal intensity" which is the ratio of amplitude of peak rotavirus activity (i.e., peak monthly prevalence of rotavirus) to the average annual prevalence of rotavirus. This ratio reduces noise from months with little or no rotavirus testing in some settings. Higher seasonal intensity reflected greater deviation from the annual mean, and thus greater seasonal variation. We also explored the seasonality patterns of each site by measuring the amplitude (peak – trough/peak) and primary peak timing of the 'average' year calculated using Fourier analysis. Briefly, by this method we extracted the frequencies of the first (annual), second (semi-annual) and third (quarterly) harmonics in the data, which were then summed to produce the seasonal signature of the series.(13) Amplitudes and primary peak timings of each site were inspected against their corresponding latitudes.(14)

We used multivariable linear regression to identify independent variables that were potentially associated with the seasonal intensity of rotavirus. Possible predictors were identified on the basis of previous studies and hypotheses for explaining rotavirus seasonality. These included temperature, rainfall, altitude, geographic location (latitude), population density, and level of country development as measured by 2001's Gross National Income [GNI] per capita adjusted for purchasing power parity, retaining all variables in the final model. Birth rate was considered as a potential explanatory variable but was not included due to collinearity with GNI. Including study size in the model did not alter the findings and thus was not retained in the final model. Data on weather, latitude, and altitude were abstracted from Weatherbase(15) and the World Weather Information Service.(16) For cities that were not listed in the weather databases, meteorological information was based on a nearby city within the same climatic region. For studies that reported aggregate results of multiple cities, the average weather pattern was calculated. GNI per capita based on purchasing power parity was obtained from the World Bank.(17) The year of 2001 was chosen as it is the average year of the focused studies. Analyses were conducted using Matlab R2007b, and SAS 9.1.

RESULTS

We reviewed 522 abstracts to identify a total of 186 potential studies, from which 99 studies (representing 153 separate study sites) met the inclusion criteria of our analysis (Table 1).

These studies represented all six regions of the world, with sites being most common in Asia (59%) and South America (20%), and less common in Europe (8%), Africa (7%), North/Central America (4%), and Oceania (3%). Most studies had similar methodology in that they followed the WHO recommendations for conducting rotavirus surveillance, used enzyme linked immunoassays to detect rotavirus, and limited the sample population to children less than 5 years of age. Studies reported data from the hospital setting (83%), outpatient setting (3%), or both (14%). In total, these studies reported data on ~428,000 samples of stool from children with diarrhea, of which ~111,000 (26%) tested positive for rotavirus.

When studies were examined by regions, in general, detection of rotavirus occurred year-round in Africa, Asia, and South America, with some month-to-month fluctuations (Figure 1). In these continents, the mean prevalence of rotavirus ranged between 31%–48% during peak month and 15%–23% during the nadir (i.e., lowest prevalence) month. In contrast, seasonality was stronger in Europe, North America, and Oceania, with prevalence of disease ranging between 37%–60% during peak winter months and 4%–11% during the nadir summer months. Detection of rotavirus overlapped with the winter months (November–April) in higher Northern latitudes, and the peak times in the tropical belt were also in phase with the peak times of higher latitudes (Figures 2&3). In contrast, peak prevalence in the Southern hemisphere (below 10° South) typically occurred between May and October, the winter months in this hemisphere. The intensity of seasonality was quite strong through all latitudes, although overall a bit lower in the tropical belt (Figures 4&5), where the monthly prevalence never dropped below 33%, compared with countries further north or south of these latitudes where minimum monthly prevalence ranged between 11%–22% (Figure 2).

When countries were grouped according to their level of economic development (Figure 6), the low- and low-middle income countries had a higher mean minimum prevalence of rotavirus at 31% during the nadir month compared with 14% in high-income countries and 18% in upper-middle income countries. In the multivariate regression model, no single factor explained most of the seasonality at this ecological level (R^2=0.13, $P<0.001$). Among considered factors, the country GNI emerged as the strongest predictor of the seasonality intensity (P=0.001), after adjusting for latitude, yearly rainfall, average, temperature, altitude, and population density. Although latitude and climate were not significant predictors of the seasonality intensity in the multivariate model overall, a distinct pattern existed with regard to the timing of the peak prevalence of rotavirus disease (Figures 3&6) which was not assessed in the model.

The country-specific data indicated that rotavirus infection had a predictable annual pattern in some countries while in others peak timing of infection was more sporadic (Figures 6&7). For instance, some studies reported year-round prevalence of rotavirus disease with possible peaks during disparate months (e.g., Vietnam, China), while others had most rotavirus events confined to a few months of the year (e.g., El Salvador, United States, Japan). Neither latitude nor the country's level of economic development perfectly explained seasonality. For example, year-round disease was common in several poor countries closer to the equator (e.g., Indonesia, Vietnam, Cambodia), whereas other poor countries had prominent seasonal variability (e.g., El Salvador, Kenya, and Philippines) (Figure 8). Likewise, among poor countries >37° North of the equator, year-round disease was present in some regions (e.g., Ukraine, Mongolia, Tajikistan, Kyrgyzstan), but others also had marked seasonal variability (e.g., Georgia, Uzbekistan). Interestingly, year-round circulation of rotavirus was not confined to low-income countries in the tropics, but was also observed in several upper-middle and high-income countries (Figures 9&10) from various regions and latitudes (e.g., Taiwan, South Korea, Brazil, Iran, Oman, and Malaysia). The year-round patterns of rotavirus disease were similar among studies conducting surveillance for 12 months compared to those conducting surveillance for more than 12 months, indicating that this year-round pattern was not due to averaging of prevalence over multiple years with potentially different timing of peak incidence.

DISCUSSION

In 1990, Cook et al. demonstrated that rotavirus had a distinct seasonal peak in countries with temperate climates but was year-round in the tropics.(3) Our review of a large body of data published since the paper by Cook et al. identified that such a clear distinction between seasonal patterns in tropical and temperate settings may not exist, as many countries in the tropics exhibited very seasonal disease patterns while several temperate countries showed year-round disease. The level of country development was a stronger predictor of seasonal intensity of rotavirus disease than latitude or geographical location per se —poorer countries, particularly those in Africa, Asia and South America had lesser seasonal variation in disease than more developed countries from Europe, North America, and Oceania, even after taking into account local climate and geographical location. These data are not in complete disagreement with findings by Cook et al. in that tropical countries are in general less developed than those in temperate regions. Our findings are also consistent with a recent modeling study by Pitzer et al.(18) which demonstrated that high transmission rates and high birth rates, factors common to poor countries, explained, in part, a relative lack of seasonality in these countries. However, on closer examination of data from individual countries, we found several exceptions to these general patterns, and thus it is possible that factors other than income level and transmission patterns could also influence seasonal patterns of rotavirus disease to some extent.

Some data have suggested that local climatologic factors may be associated with seasonality of rotavirus disease, with increased incidence during cool, dry seasons, particularly in settings where the annual rotavirus epidemic coincides with the winter season.(5, 19, 20) Because survival of infective rotavirus is favored in cooler conditions with low relative humidity, it has been hypothesized that a relative drop in humidity and rainfall combined with drying of soils might increase the aerial transport of dried, contaminated fecal material.(21, 22) In our analysis, detection of rotavirus overlapped with the cooler months in higher latitudes but, surprisingly (given that the winter concept is less common closer to the equator) peak times of rotavirus detection in the tropical belt were generally in phase with the peak times of higher latitudes (Figure 3). While subtle changes in local climate may play a role in explaining seasonal cycling of rotavirus disease in some settings, the gross differences in seasonal prevalence of rotavirus disease globally cannot be attributed to climate alone. For example, several countries with temperate climates such as Ukraine(23) and Kyrgyzstan(24) had year-round presence of rotavirus disease whereas disease tends to be highly concentrated during the winter months in other temperate regions of North

America(25) and Western Europe(26, 27). Likewise, several poor tropical countries such as Kenya(28) and El Salvador(29) also have notable seasonal disease similar to some wealthier countries in temperate climates such as the US. The fact that rotavirus peaks occur on a yearly basis would suggest that some factor that cycles annually (potentially related to weather), must play a role underpinning the timing and regularity of patterns. However, any single explanation for seasonal differences in rotavirus disease globally is difficult to reconcile with these observations.

At a regional level, many factors may interact and explain seasonality including climate, transmission patterns, host behavior, and susceptibility. The influence of these factors may also be context specific. It is possible that multiple factors related to transmission interact in some settings and have opposing climatic influences. For instance, contaminated water may be an important source of transmission in settings with poor sanitation.(30, 31) Rotavirus can be isolated from water sources, and waterborne outbreaks of rotavirus have been described.(31–34) Furthermore, some studies have noted secondary seasonal peaks in rotavirus incidence associated with periods of high rainfall and flooding.(6, 35) The waterborne transmission route may dominate during times of increased rainfall in such settings, whereas more direct forms of transmission may dominate during the cooler, drier seasons (when virus survival is increased) across all settings. Rotavirus strains also tend to be more diverse in low-income settings.(36) Although no data exist assessing the variation in seasonality between the different rotavirus serotypes, factors driving the global seasonality of influenza have been determined to differ between the specific types and subtypes of the influenza virus.(37) Similar differences between different strains of rotavirus, if they were to exist, might partly explain the weaker seasonality in low-income settings.

Some limitations must be considered when interpreting our results. While we provided a descriptive account of differences in seasonality of rotavirus by region, we did not explicitly account for factors such as local transmission dynamics; a closer examination of regional data may provide an explanation for the timing of onset and variation in disease in any given country or geographic region. Furthermore, we only examined associations between a crude indicator of seasonality and possible predictors. A more detailed examination of the associations between annual variation in rotavirus prevalence in each setting and possible predictors, taking into account population immunity, possible lags, and the non-linear effects of transmission(8), was beyond the scope of the current study and would require more detailed data. Heterogeneity in data quality is likely to exist given the large number of studies. However, of specific importance to our objective is that most studies in the past decade have employed validated diagnostic assays and a similar case-definition for diarrhea, and were conducted for a minimum of 12 calendar months among children <5 years of age. Another potential limitation is that most studies presented monthly prevalence of rotavirus detection (proportion of tests positive) among children with diarrhea rather than the actual number of events. Monthly prevalence of rotavirus might be affected by the incidence of non-rotavirus pathogens, which will influence the number of acute gastroenteritis events that are tested. However, our conclusions were unchanged when we assessed this potential effect in a subset of studies that presented both case-counts and percent of tests positive for rotavirus. Lastly, the number of children enrolled in individual studies varied markedly. To account for the undue influence of studies with a smaller sample, we used weighted averages when pooling data across regions; however, patterns of seasonality remained unchanged when we used unweighted averages.

Many countries, mostly developed countries with seasonal disease, have already introduced rotavirus vaccines, and introductions are expected in poorer regions of Asia and Africa in coming years.(38) Changes in seasonality of rotavirus disease after large-scale rollout of rotavirus vaccines particularly in countries with year-round disease versus highly seasonal disease should allow us to test the various proposed hypotheses for the seasonal cycling of rotavirus disease. For example, Pitzer et al have demonstrated through modeling that variation in birth rates within the US strongly influences the timing and spread of the annual rotavirus epidemic.(39) Since the introduction of vaccine in the US, studies have observed a remarkable alteration in the timing of the annual winter epidemic and spatiotemporal spread of rotavirus disease(40), which confirmed the influence of birth rates on seasonality in the US in so far as vaccination is effectively similar to reducing the birth rate by reducing the number of fully susceptible children entering the population. Under the hypothesis that the apparent lack of seasonality in some countries is related to higher birth rates, vaccination could alter the seasonal cycling of rotavirus in some developing countries and lead to the appearance of more strongly seasonal disease during the first few years after vaccine introduction(18). Use of vaccine particularly in countries with year-round disease may help elucidate the competing explanations of seasonality, thereby providing insights into the transmission dynamics of rotavirus.

In summary, marked differences in seasonal prevalence of rotavirus disease occur globally. Observations from several countries challenged the traditional dogma that rotavirus disease is seasonal in temperate settings but not in tropical countries. We found that country income level was somewhat more predictive of the likelihood of having seasonal disease than other factors. However, the observations of distinctly different seasonal patterns of rotavirus disease in some countries with similar geographical location, climate and level of development are difficult to reconcile, indicating that a single unifying explanation for variation in seasonality of rotavirus disease is unlikely. Higher birth rates and higher transmission rates have emerged as a potential explanation for sustained year-round circulation of rotavirus, but an interaction of other local factors between the host and the environment likely also contribute to the seasonality.

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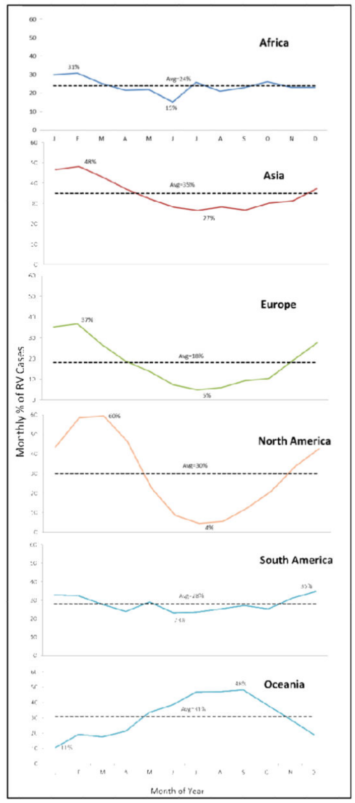

Figure 1.
Seasonal variation in rotavirus prevalence globally by region, 1996–2009.

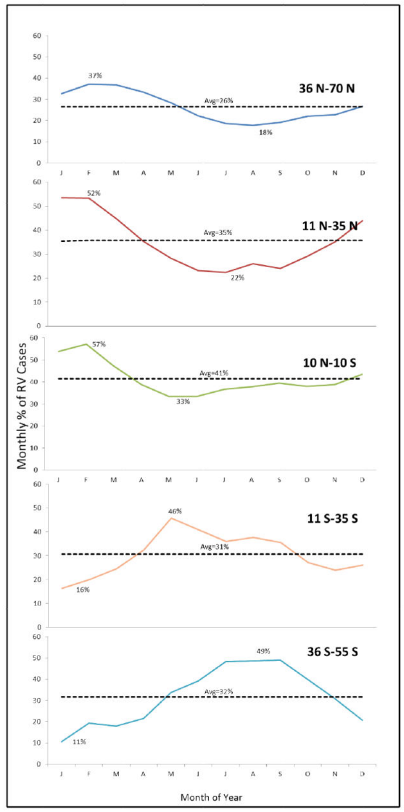

Figure 2.
Seasonal variation in rotavirus prevalence globally by latitude, 1996–2009.

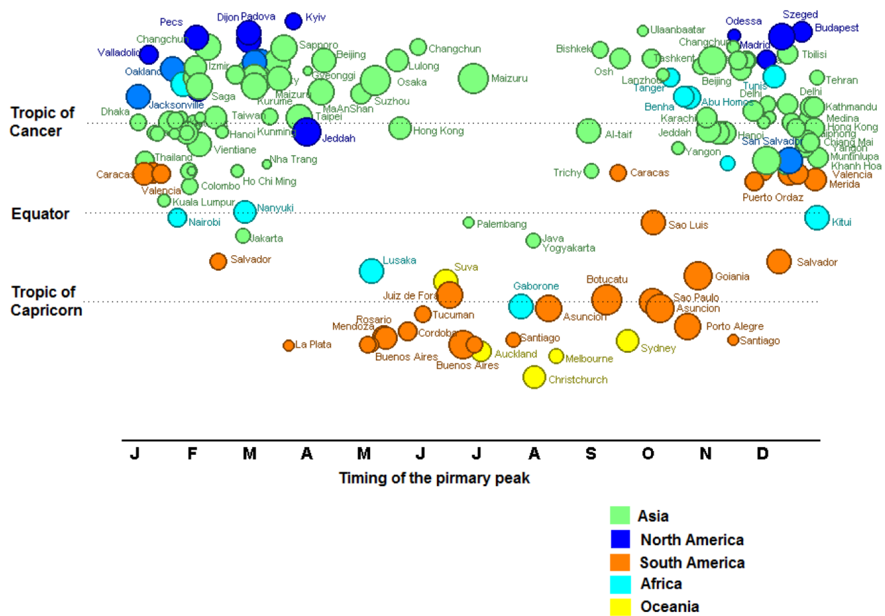

Figure 3. Timing of the primary peak of rotavirus disease globally, by latitude

Colors denote continents to which each point belongs and size of circle is proportion to the number of months rotavirus was in circulation.

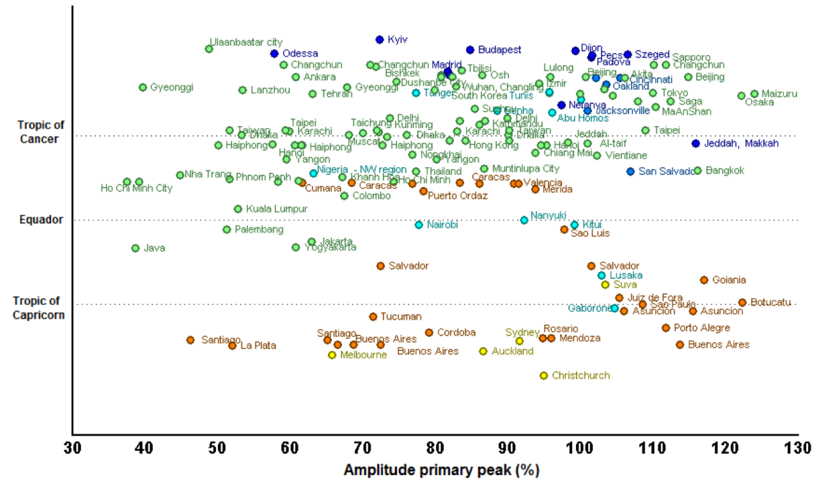

Figure 4. Amplitude of the primary peak of the seasonal signature of the series as a function of latitude

Amplitude is peak-trough/peak ratio. Colors denote continents to which each point belongs.

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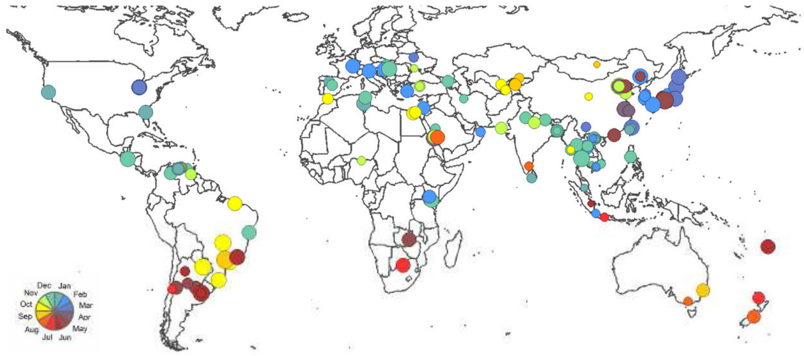

Figure 5.

Map with the same information, but here the relative amplitudes are expressed in circle sizes.

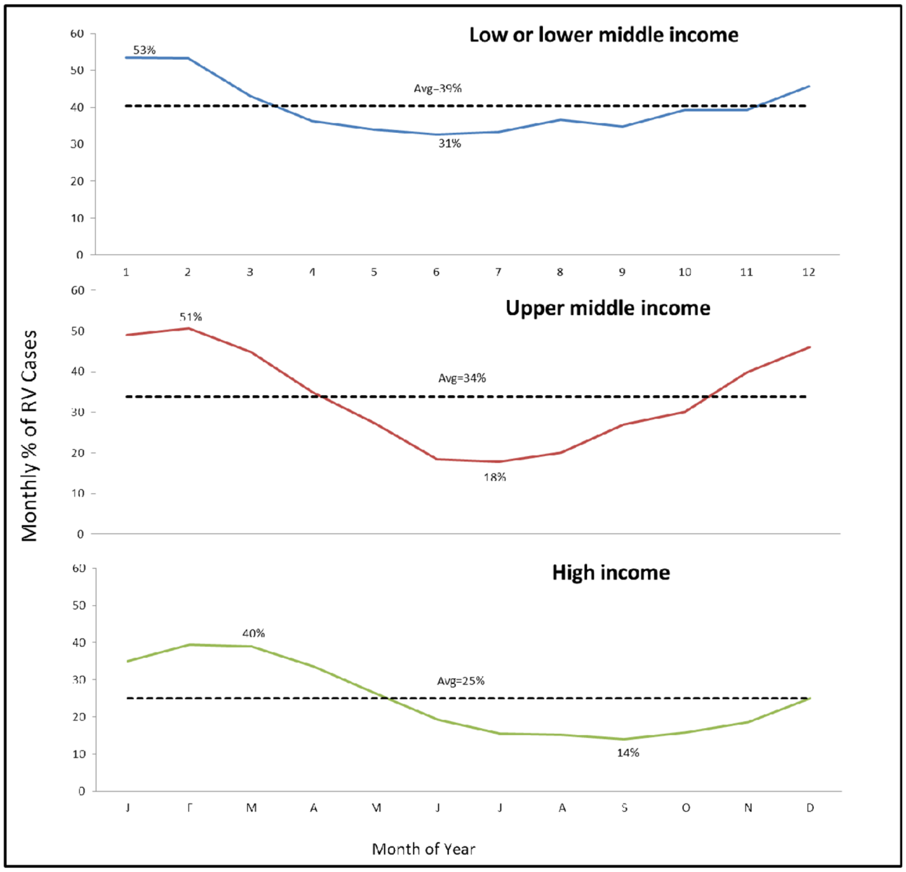

Figure 6. Seasonal variation in rotavirus in tropical and northern temperate zones, by World Bank income groups

We restricted the analysis to studies conducted in the Northern Hemisphere and the tropical belt (i.e., latitudes 10° North and 10° South of the equator) to avoid falsely representing seasonality by summing monthly prevalence across regions with peak rotavirus detections during opposing seasons (which would result in a bias towards weaker seasonality).

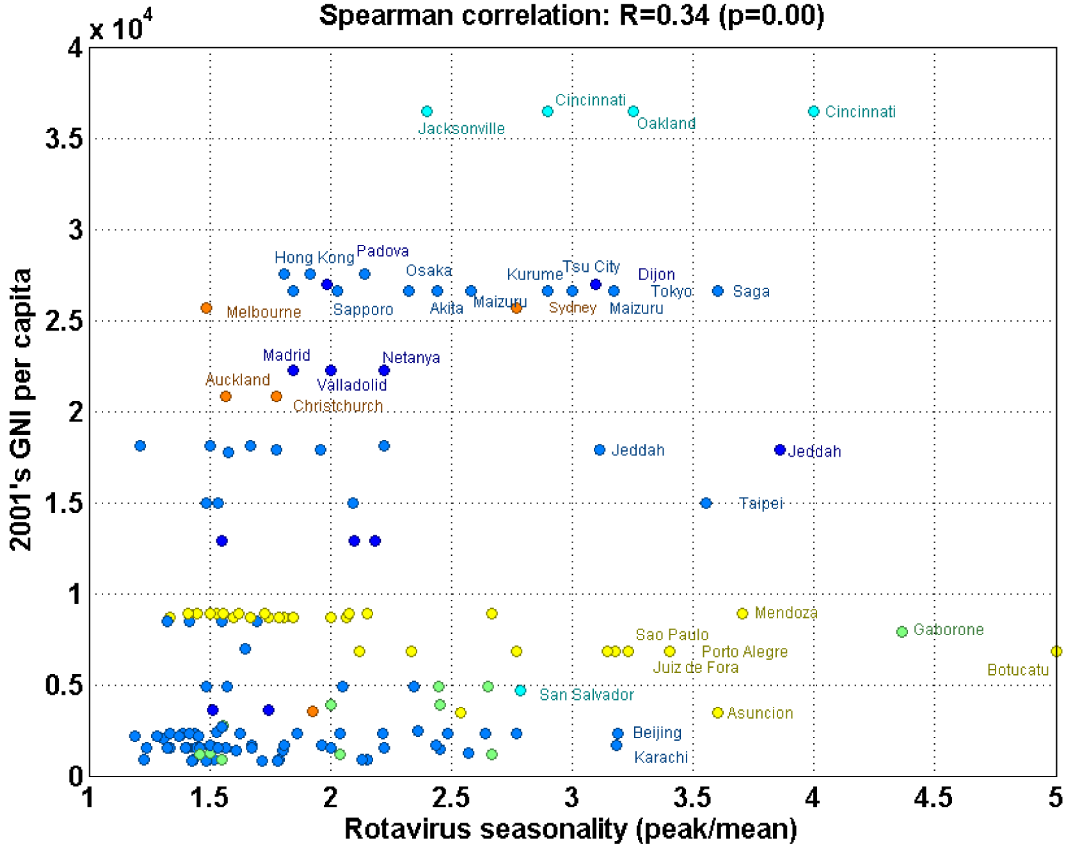

Figure 7. Scatter plot of gross national income per capita plotted against the strength of rotavirus seasonality

Gross national income per capita is adjusted for purchasing power parity. Strength of seasonality was defined by the “seasonality ratio” (peak/mean prevalence). Colors denote continents to which each point belongs. Site legends are displayed for “outliers” (where values are more than one standard deviation above the average).

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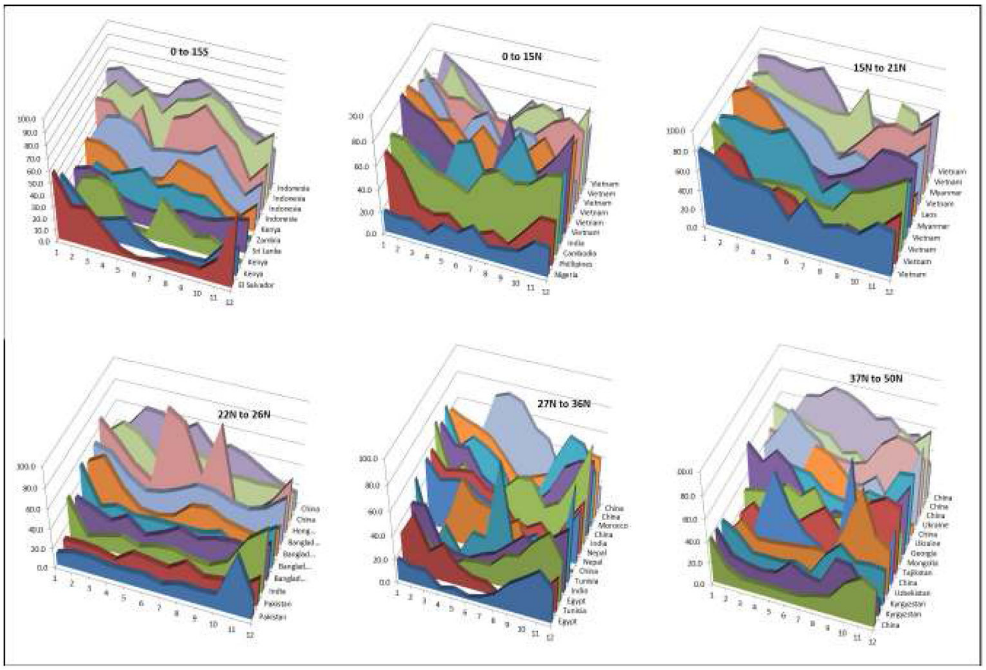

Figure 8.

Seasonality in low and low-middle income countries, by latitude.

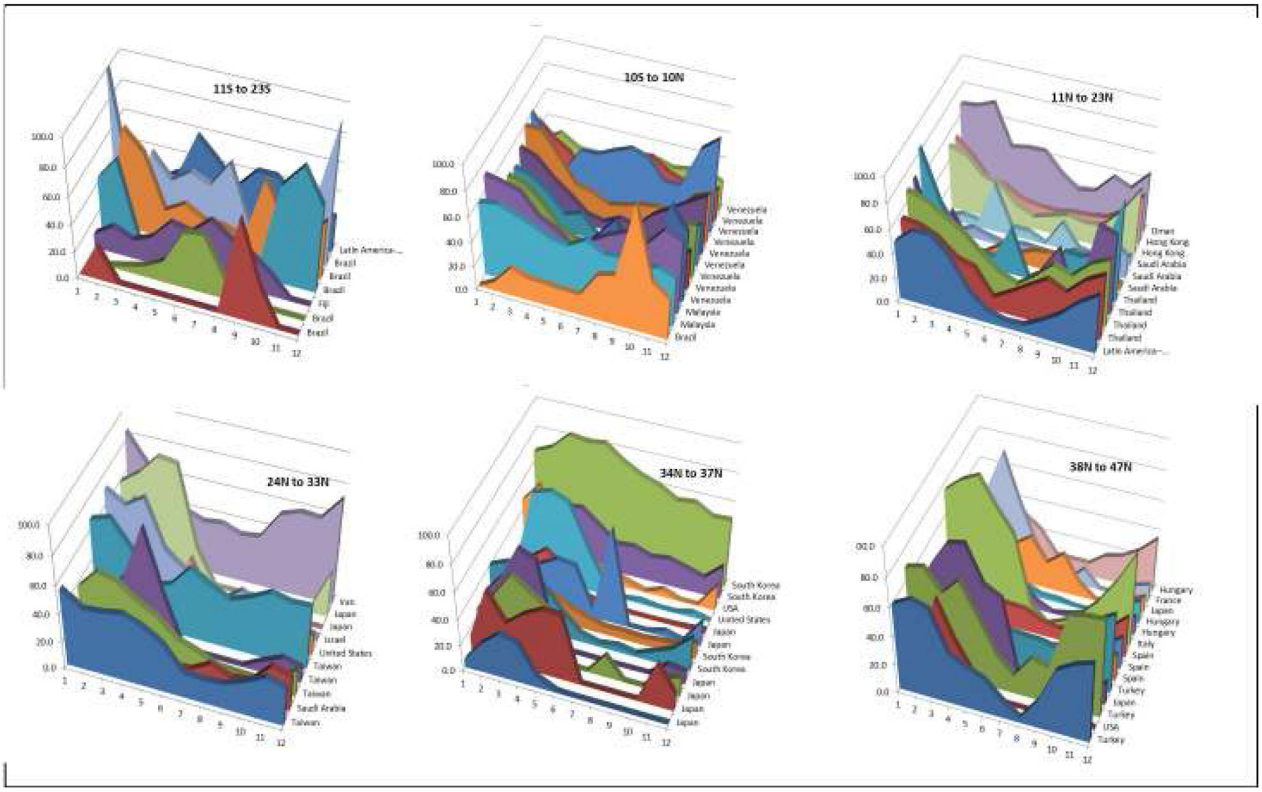

Figure 9.
Seasonality in high-middle and high-income countries, by latitude.

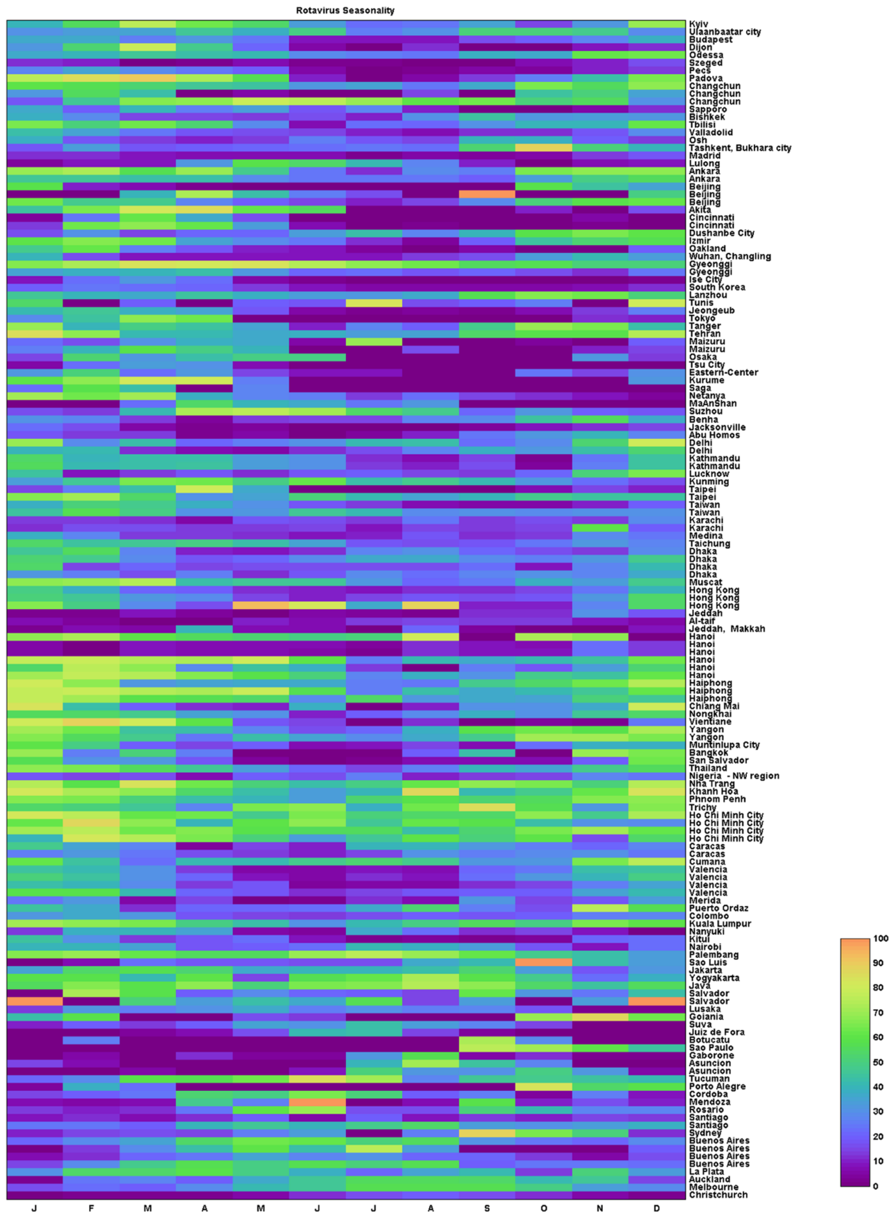

Figure 10. Visualization of relative detection of rotavirus per month in each site globally, sorted by latitude

The colors represent the monthly prevalence of rotavirus among diarrhea cases, as indicated by the color bar.

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Table 1

Summary of studies published between 1999–2010 that assessed rotavirus seasonality globally

Ref	Country	City	Study Dates	Age	Site	No. AGE	%RV	Peak RV month	GNI
	AFRICA								
(41)	Egypt	Abu Homos	05/2000–05/2002	<5	**H**	714	10%	11	2016
(41)	Egypt	Benha	05/2000–05/2002	<5	**H**	561	23%	11	2016
(42)	Morocco	Tanger, Rabat, Oujda, Benimellal	06/2006–07/2007	<5	**H**	314	44%	1	2696
(43)	Nigeria	NW region	07/2002–07/2004	<5	**H**	869	18%	11	1393
(44)	Tunisia	Eastern-Center	10/2003–09/2005	<5	**B**	638	21%	2	3680
(28)	Kenya	Nairobi	08/1991–07/1994	<6	**H**	656	28%	7	783
(28)	Kenya	Kitui	08/1991–07/1994	<6	**H**	490	14%	1	783
(28)	Kenya	Nanyuki	08/1991–07/1994	<6	**H**	285	22%	3	783
(45)	Zambia	Lusaka	01/1992–12/1992	<5	**H**	1067	24%	5	1053
(46)	Botwsana	Gaborone	03/2001–02/2002	<5	**H**	346	9%	8	5630
(47)	Tunisia	Tunis	01/2007–12/2007	<5	**H**	117	26%	7	3680
	ASIA								
(48)	Malaysia	Kuala Lumpur	01/2001–04/2003	<5	**H**	2668	47%	2	7921
(49)	Thailand	Country-wide	07/2001–06/2003	<5	**B**	1950	43%	1	4046
(50)	Saudi Arabia	Medina	04/2004–04/2005	<5	**B**	984	19%	1	18718
(51)	Indonesia	Palembang, Jakarta, Bandung, Yogyakarta, Denpasar, Mataram	01/2006–12/2006	<5	**B**	2416	59%	7	2150
(52)	Indonesia	Jakarta	02/2004–02/2005	<5	**O**	1660	45%	3	2150
(53)	Oman	Muscat, Salalah, Sohar, Rustaq, Nizwa, Ibra, Sur, Ibri	07/2006–06/2008	<5	**H**	3470	49%	3	17884
(54)	Phillipines	Muntinlupa City	01/2005–12/2006	<5	**B**	2946	21%	1	2063
(55)	Japan	Maizuru, Tokyo, Sapporo, Saga and Osaka	07/2006–06/2007	<10	**H**	628	20%	7	39853
(56)	China	Various cities throughout	08/2003–07/2007	<5	**H**	7846	48%	1	3213
(57)	Iran	Tabriz, Mashhad, Tehran, Shiraz, Bandar Abbas	05/2006–04/2007	<5	**H**	2198	59%	1	4651
(58)	Uzbekistan	Tashkent, Bukhara city	01/2005–12/2006	<5	**H**	3537	30%	10	948
(59)	South Korea	Gyeonggi	01/2001–12/2005	All ages	**B**	10028	67%	3	19422
(23)	Georgia	Tbilisi	01/2007–12/2007	<5	**H**	703	40%	1	2948
(23)	Tajikstan	Dushanbe City	01/2007–12/2007	<5	**H**	702	38%	11	468

Ref	Country	City	Study Dates	Age	Site	No. AGE	%RV	Peak RV month	GNI
(60)	Mongolia	Ulaanbaatar city	03/2005–02/2007	<5	**H**	1152	40%	9	2052
(60)	Sri Lanka	Colombo	03/2005–02/2007	<5	**H**	1806	24%	2	2007
(61)	Nepal	Kathmandu	11/2005–10/2007	<5	**H**	1139	33%	1	468
(61)	Nepal	Kathmandu	11/2005–10/2007	<5	**H**	1139	33%	1	468
(62)	Turkey	Ankara, Istanbul, Izmir, and Adana	06/2005–06/2006	<5	**H**	338	53%	2	10007
(63)	India	Delhi	12/2005–11/2007	<5	**H**	633	37%	12	1054
(63)	India	Trichy	12/2005–11/2007	<5	**H**	406	53%	9	1054
(64)	Japan	Tsu City	01/2003–12/2007	<5	**H**	551	46%	3	39853
(64)	Japan	Ise City	01/2003–12/2007	<5	**H**	327	59%	3	39853
(65)	Bangladesh	Dhaka	01/2001–05/2006	<5	**H**	19039	24%	2	533
(66)	Pakistan	Karachi	06/2005–05/2007	<5	**O**	575	17%	12	1031
(24)	Kyrgyzstan	Bishkek	01/2005–12/2007	<5	**H**	1959	29%	9	909
(24)	Kyrgyzstan	Osh	01/2005–12/2007	<5	**H**	1797	22%	9	909
(67)	China	Changchun, Lulong, Lanzhou	01/2006–12/2007	<5	**H**	2328	52%	12	3213
(68)	Taiwan	Various	01/2005–12/2007	<5	**H**	3435	25%	2	18000
(69)	Vietnam	Haiphong	09/2006–08/2007	<5	**H**	978	52%	1	1019
(70)	Cambodia	Phnom Penh	03/2005–02/2007	<5	**H**	2817	45%	12	660
(71)	Laos	Vientiane	03/2005–02/2007	<5	**H**	1158	55%	2	790
(72)	Myanmar	Yangon	01/2004–12/2005	<5	**H**	2179	56%	12	578
(73)	Indonesia	Java	08/2001–04/2004	<3	**H**	1321	53%	8	2150
(74)	South Korea	Gyeonggi	07/2001–06/2002	<18	**H**	1031	27%	4	19422
(75)	Taiwan	Taipei	01/2004–03/2005	<14	**H**	201	26%	4	18000
(76)	Bangladesh	Dhaka	01/1993–12/2004	<5	**B**	18300	33%	1	533
(77)	China	Wuhan, Changling	12/2000–4/2006*	All ages	**B**	3174	16%	11	3213
(78)	Hong Kong	Hong Kong	04/2001–3/2003	<5	**H**	5881	30%	1	32900
(79)	Japan	Akita	01/2001–12/2002	<5	**H**	422	58%	4	39853
(80)	India	New Delhi	08/2000–07/2001	<5	**H**	584	23%	12	1054
(81)	Bangladesh	Dhaka	02/1993–06/1994	<5	**H**	814	20%	1	533
(82)	Turkey	Ankara	03/1999–12/2002	<16	**H**	1099	37%	12	10007
(83)	Saudi Arabia	Jeddah	1/1992–12/1992	<5	**H**	1031	43%	11	18718
(83)	Saudi Arabia	Al-taif	07/1992–06/1993	<5	**H**	354	42%	8	18718

Ref	Country	City	Study Dates	Age	Site	No. AGE	%RV	Peak RV month	GNI
(84)	Thailand	Chiang Mai	01/1995–12/1996	Pedi atric	**H**	164	34%	1	4046
(85)	Pakistan	Karachi	01/1990–12/1997	<5	**H**	818	14%	11	1031
(86)	Vietnam	Hanoi	07/1998–06/2000	<5	**H**	1233	53%	5	1019
(86)	Vietnam	Hanoi	07/1998–06/2000	<5	**H**	390	47%	2	1019
(86)	Vietnam	Haiphong	07/1998–06/2000	<5	**H**	886	60%	5	1019
(86)	Vietnam	Nha Trang	07/1998–06/2000	<5	**H**	589	59%	3	1019
(86)	Vietnam	Ho Chi Minh City	07/1998–06/2000	<5	**H**	1724	57%	1	1019
(86)	Vietnam	Ho Chi Minh City	07/1998–06/2000	<5	**H**	946	58%	2	1019
(87)	South Korea	Jeongeub	07/2002–06/2004	<5	**H**	2232	21%	2	19422
(88)	China	Taiwan	04/2001–03/2003	<5	**H**	2600	43%	2	3213
(89)	China	MaAnShan	08/2001–07/2003	<5	**H**	158	28%	4	3213
(89)	China	Beijing	08/2001–07/2003	<5	**H**	70	36%	9	3213
(89)	China	Lulong	08/2001–07/2003	<5	**H**	667	45%	5	3213
(89)	China	Suzhou	08/2001–07/2003	<5	**H**	703	49%	5	3213
(89)	China	Changchun	08/2001–07/2003	<5	**H**	904	65%	5	3213
(89)	China	Kunming	08/2001–07/2003	<5	**H**	647	46%	3	3213
(90)	Myanmar	Yangon	01/2002–12/2003	<5	**H**	1736	53%	10	578
(91)	Vietnam	Hanoi	07/2000–06/2003	<5	**H**	1690	56%	2	1019
(91)	Vietnam	Haiphong	07/2000–06/2003	<5	**H**	1095	44%	1	1019
(91)	Vietnam	Khanh Hoa	07/2000–06/2003	<5	**H**	625	50%	8	1019
(91)	Vietnam	Ho Chi Minh City	07/2000–06/2003	<5	**H**	1508	59%	2	1019
(91)	Vietnam	Ho Chi Minh City	07/2000–06/2003	<5	**H**	891	62%	2	1019
(92)	Hong Kong	Hong Kong	01/1987–12/1996	<5	**H**	7822	28%	12	32900
(93)	Bangladesh	Dhaka	01/1990–12/1993	<5	**B**	7709	20%	12	533
(9)	China	Beijing, Changchun, Lulong, Kunming, Ma-An-Shan, Suzhou	08/2001–07/2002	<5	**H**	2079	44%	1	3213
(9)	Vietnam	Hanoi, Haiphong, Khan Hoa, Ho Chi	08/2001–07/2002	<5	**H**	1570	59%	8	1019
(9)	Taiwan	Minh City, Taipei	08/2001–07/2002	<5	**H**	1532	49%	2	18000
(9)	Thailand	Nongkhai, Maesod, Prapokklao, Ramathibodi, Hadyai, Srakaew	08/2001–07/2002	<5	**H**	992	44%	1	4046
(9)	Hong Kong	Hong Kong	08/2001–07/2002	<5	**H**	2986	28%	5	32900
(9)	Malaysia	Kuala Lumpur, Sarawak	08/2001–07/2002	<5	**H**	1374	57%	1	7921
(9)	Indonesia	Yogyakarta, Purworejo	08/2001–07/2002	<5	**H**	577	52%	8	2150

Ref	Country	City	Study Dates	Age	Site	No. AGE	%RV	Peak RV month	GNI
(94)	China	Lanzhou	01/2001–12/2006	<5	**H**	1019	52%	10	3213
(95)	Turkey	Izmir	01/2000–01/2001	<5	**H**	920	40%	2	10007
(96)	Taiwan	Taichung	12/2004–06/2006	<5	**H**	763	46%	1	18000
(97)	India	Lucknow	09/2004–04/2008	<3	**H**	412	19%	12	1054
(98)	Japan	Sapporo	07/1984–06/1999	<14	**H**	445	49%	3	39853
(98)	Japan	Tokyo	07/1984–06/1999	<14	**H**	1172	67%	3	39853
(98)	Japan	Maizuru	07/1984–06/1999	<14	**H**	2311	50%	3	39853
(98)	Japan	Osaka	07/1984–06/1999	<14	**H**	519	54%	2	39853
(98)	Japan	Kurume	07/1984–06/1999	<14	**H**	1188	69%	3	39853
(98)	Japan	Saga	07/1984–06/1999	<14	**H**	296	76%	2	39853
(99)	Thailand	Bangkok	04/2001–03/2002	<5	**H**	85	48%	11	4046
(100)	South Korea	Country-wide	09/2000–08/2007	All ages	**H**	164081	12%	2	19422
	EUROPE								
(101)	Israel	Netanya, Hadera, Haifa	11/2007–10/2008	<5	**H**	412	34%	3	28190
(102)	Italy	Padova	10/2004–09/2005	<5	**B**	725	46%	3	38047
(23)	Ukraine	Kyiv	01/2007–12/2007	<5	**H**	947	49%	3	3879
(23)	Ukraine	Odessa	01/2007–12/2007	<5	**H**	1022	41%	12	3879
(103)	Spain	Valladolid	01/2000–12/2004	<5	**H**	2233	24%	1	35098
(104)	Saudi Arabia	Jeddah, Makkah, Riyadh	09/2002–08/2003	<6	**B**	1000	6%	4	18718
(105)	Spain	Country-wide	01/1999–12/2000	All ages	**H**	32541	14%	2	35098
(106)	Hungary	Budapest	01/1993–12/1996	<14	**H**	6022	26%	12	14387
(106)	Hungary	Pecs	01/1993–12/1996	<14	**H**	845	11%	2	14387
(106)	Hungary	Szeged	01/1993–10/1996	<14	**H**	2315	12%	12	14387
(27)	Spain	Madrid	10/1998–10/2002	<5	**H**	3760	31%	12	35098
(26)	France	Dijon	10/2004–09/2005	<5	**H**	218	33%	3	44972
	NORTH & CENTRAL AMERICA								
(107)	USA	Cincinnati	03/1999–05/2000	<5	**H**	199	37%	3	45836
(107)	USA	Oakland	03/1999–05/2000	<6	**H**	83	46%	2	45836

Ref	Country	City	Study Dates	Age	Site	No. AGE	%RV	Peak RV month	GNI
(108)	United States	Jacksonville	12/1991–11/1995	<1	**B**	194	49%	1	45836
(29)	El Salvador	San Salvador	05/2001–04/2002	<5	**H**	322	21%	12	3499
(25)	United States	Cincinnati and Durham	02/2005–06/2006	<5	**B**	1601	44%	3	45836
(109)	Latin America--north hemisphere*	El Salvador, Guatemala, Honduras, Venezuela, Guyana	01/2006–12/2007	<5	**H**	15071	41%	3	4114[a]
	OCEANIA								
(110)	New Zealand	Auckland, Christchruch, Wellington	05/1998–04/2000	<3	**H**	1138	43%	7	30447
(111)	Fiji	Suva	01/2006–12/2007	<5	**H**	454	39%	7	4018
(112)	Australia	Melbourne	04/1980–03/1993	<14	**H**	3503	42%	9	46574
(113)	Australia	Sydney	07/1997–06/1998	<5	**B**	412	14%	9	46574
(114)	New Zealand	Christchurch, Wellington	05/1998–04/2000	<3	**H**	1138	43%	8	30447
	SOUTH AMERICA								
(115)	Chile	Iquique, Santiago	08/2004–10/2005	<5	**O**	1313	14%	5	9147
(116)	Brazil	Goiania	08/2005–08/2006	<5	**B**	98	42%	11	8136
(116)	Brazil	Porto Alegre	08/2005–08/2006	<5	**B**	56	21%	10	8136
(116)	Brazil	Salvador	08/2005–08/2006	<5	**B**	147	38%	2	8136
(116)	Brazil	Sao Paulo	08/2005–08/2006	<5	**B**	209	54%	9	8136
(117)	Venezuela	Merida	06/1993–05/1995	<5	**H**	377	15%	12	11444
(117)	Venezuela	Valencia	06/1998–05/2000	<5	**H**	4414	25%	1	11444
(117)	Venezuela	Cumana	06/1993–05/1995	<5	**H**	376	46%	12	11444
(117)	Venezuela	Puerto Ordaz	06/1993–05/1995	<5	**H**	336	29%	11	11444
(117)	Venezuela	Caracas	06/1993–05/1995	<5	**H**	1239	31%	1	11444
(118)	Venezuela	Caracas	01/1988–12/1993	<3yr	**B**	2101	26%	2	11444
(119)	Argentina	Tucuman	10/1996–9/1998	<3	**H**	435	53%	6	8027
(119)	Argentina	Mendoza	10/1996–9/1998	<3	**H**	151	23%	6	8027
(119)	Argentina	La Plata	10/1996–9/1998	<3	**H**	188	48%	4	8027
(119)	Argentina	Rosario	10/1996–9/1998	<3	**H**	174	34%	6	8027
(119)	Argentina	Cordoba	10/1996–9/1998	<3	**H**	231	32%	6	8027
(120)	Argentina	Buenos Aires	08/1997–07/1999	<3	**H**	1133	39%	5	8027
(120)	Chile	Santiago	08/1997–07/1999	<3	**H**	1739	34%	8	9147

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Ref	Country	City	Study Dates	Age	Site	No. AGE	%RV	Peak RV month	GNI
(120)	Venezuela	Valencia	08/1997–07/1999	<3	**H**	2929	29%	1	11444
(121)	Argentina	Buenos Aires	09/1997–08/1998	<3	**O**	66	26%	7	8027
(122)	Paraguay	Asuncion	01/1999–03/2000	<3	**B**	220	32%	8	2688
(123)	Brazil	Botucatu	06/1997–05/1998	<5	**H**	54	41%	9	8136
(124)	Venezuela	Valencia	01/1998–12/2002	<5	**O**	9109	20%	1	11444
(124)	Venezuela	Valencia	01/1998–12/2002	<5	**H**	2879	31%	1	11444
(125)	Brazil	Sao Luis	06/1997–06/1999	<3	**H**	128	32%	10	8136
(126)	Paraguay	Asuncion	08/1998–12/1999	<4	**H**	393	19%	7	2688
(127)	Brazil	Salvador	11/2003–11/2004	<19	**H**	558	16%	1	8136
(128)	Argentina	Buenos Aires	01/1997–06/2003	<17	**H**	1579	27%	5	8027
(129)	Brazil	Juiz de Fora	01/1998–12/1998	<5	**B**	656	12%	7	8136
(109)	Latin America--southern hemisphere*	Bolivia, Paraguay, Chile	01/2006–12/2007	<5	**H**	4532	36%	5	4450[a]
(130)	Argentina	Buenos Aires	09/1997–08/1998	<3	**H**	648	36%	6	8027

H denotes hospitalization; O denotes outpatient visit; B denotes both; GNI denotes gross national income

[a]: individual data not presented for these countries, thus average GNI of the countries was taken.

Table 2

Results of the multiple linear regression model[a] assessing predictors of seasonality

Variable	Coefficient (β)	Standard Error	*P*
Intercept	0.7016	0.9598	0.466
Latitude	0.0200	0.0147	0.1749
Yearly rainfall	0.0001	0.0002	0.7116
Average temperature	0.0357	0.0249	0.155
Altitude	0.0002	0.0002	0.3892
GNI[b] per capita × 1000	0.0272	0.0826	0.0012
Population density	−0.0007	0.0005	0.1178

[a]: Response variable was seasonality ratio of rotavirus (peak monthly prevalence/mean prevalence). Model $R^2 = 0.13$. Study size but was also evaluated in a separate model but was not significant (P=0.47) and did not alter the current model findings.

[b]: GNI denotes gross national income adjusted for purchasing power parity