SYSTEMATIC REVIEWS Seasonality of rotavirus disease in the tropics: a systematic review and meta-analysis

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Introduction

Throughout the world, rotavirus is the single most important viral agent of acute diarrhoea in children. Rotavirus accounts for \sim 39% of all cases of severe diarrhoea and over 600 000 deaths worldwide each year.¹ Unlike many bacteriological agents of diarrhoeal illness, rotavirus occurs in both temperate and tropical areas. Rotavirus infections are universal diseases of children, regardless of the level of hygiene that prevails or the quality of food and water. Children in developed countries are infected at the same ages and as frequently as those in less developed countries.² However, an estimated 82% of the 1205 children who die each day from rotavirus disease live in the poorest countries of the world, possibly because of inadequate access to hydration therapy and a greater prevalence of malnutrition.³ A review of 43 studies from 15 countries on the African continent found rotavirus to be the single most common cause of diarrhoea, responsible for about one-quarter of all diarrhoea cases identified in both hospital patients and outpatients.⁴

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Rotavirus is believed to be spread predominantly through fecal-oral transmission, through water, person-to-person contact, or contaminated environmental surfaces, although respiratory secretions have also been speculated as a source of infection.⁵ Rotaviruses are highly infectious. Replication within the intestinal tract can result in shedding of $\ge 10^{10}$ infectious particles (PFU) per ml $(3 \times 10^{11}$ PFU/oz) of feces and the infectious dose for the human small intestine has been calculated as only \sim 10 PFU/ml (300 PFU/oz).6 Rotaviruses are very durable in the environment and can survive for weeks on surfaces and in potable and recreational water.⁷

Rotavirus exhibits distinct seasonality, and has been known as 'winter diarrhoea' in some parts of the world. 'Winter gastroenteritis' and 'winter vomiting disease' were recognized illnesses of early childhood before rotavirus was identified and found to be their cause.² However, the most recent review of the global seasonality of rotavirus infections concluded that the winter seasonality of rotavirus infections is too simple a generalization. The authors of this study systematically reviewed 34 epidemiological studies of childhood diarrhoea from a wide range of countries, and concluded that globally in temperate zones, rotavirus is certainly more common in the cooler months, but the seasonal peaks of the infections can vary broadly and occur from autumn to spring. Strict winter seasonality was common only in the Americas and was the exception in other parts of the world. In the tropics (between latitudes $23^{\circ}27'$ north and south of the equator), this seasonality, defined by calendar year, was even less distinct. Of 10 surveys conducted within 10° north or south of the equator, eight exhibited no distinct seasonal trend. Farther from the equator, at latitudes 10° to 23 $^{\circ}$ 27' north and south, five of six studies showed a distinct seasonal peak two in winter, two in the autumn and winter, and one in the autumn.²

Despite these inconclusive results for the tropical belt, many other authors have referred to clustering during the cool, dry season in the tropics. 8 In a systematic review of rotavirus in Africa, rotavirus was detected year-round in nearly every country and generally exhibited distinct peaks during the dry months. Peaks were more common during dry periods than wet periods, but this pattern was not consistent for every country.⁴ Because of the high burden of rotavirus disease in developing countries and because many of these countries lie in the tropical belt, further analysis of the seasonal patterns of rotavirus in tropical countries can shed light on the epidemiology of this important disease. Two live oral vaccines, prepared by GlaxoSmithKline (GSK) and Merck, have completed promising large scale clinical trials and are currently being introduced on a global scale. $9-12$ The next generation of rotavirus vaccines will have the greatest potential impact in developing countries where the disease burden is greatest, $3,13,14$ but more

information about the epidemiology and behaviour of rotavirus in these countries is needed to ensure high efficacy and safety of the new vaccines.¹⁵ This information on the role of climatic drivers of rotavirus transmission in the tropics is important in increasing our understanding of the epidemiology and transmission of rotavirus disease.

In their analysis, Cook et al. defined winter as December–March in the northern hemisphere and June–September in the southern hemisphere.² While this classification of season by month is appropriate for temperate climates, in tropical zones distinct seasonality might occur that does not conform to these monthly classifications. In the tropics, seasonality may be driven by pressure belts and local air circulation patterns rather than changes in the amount of sunlight during different parts of the year. Therefore local climatological factors might provide more insight into seasonal patterns of rotavirus infection in this region of the world.

At the time that Cook et al. carried out their review, attempts to relate rotavirus disease incidence to climatological factors such as rainfall, humidity and temperature had not provided any conclusive results.² In 16 years since the publication of their global review, many more studies have been carried out on rotavirus incidence, in anticipation of a vaccine for this disease. For example, a recent study compared hospital admissions for rotavirus with climatic factors in three Australian cities, finding that higher temperature and humidity in the previous week were associated with a decrease in rotavirus admissions.¹⁶ In an effort to increase our understanding of the transmission and epidemiology of rotavirus disease, this paper updates the knowledge of seasonality of rotavirus infection in tropical countries through a systematic review and meta-analysis of the relationship between monthly rotavirus prevalence and climatological variables (temperature, rainfall and relative humidity) for those same months.

Methods

Search strategy & selection criteria

Studies published between 1974 and 1988 were identified by Cook et $al.^2$ and those carried out from 1988 through December 2005 were identified through a PubMed search for 'rotavirus and season.' Additionally, reference lists from several key reviews of rotavirus epidemiology were scanned for identification of relevant papers.^{3,4,7}

The criteria for study selection used by Cook et al. included: (i) conducted continuously for 1 year or more; (ii) more than 50 confirmed cases of rotavirus diarrhoea reported; and (iii) monthly data on the proportion of all patients with diarrhoea caused by rotavirus described.² These same criteria were employed, although total number of monthly rotavirus cases was used, rather than proportion of diarrhoea patients testing

positive for rotavirus, to avoid specious results driven by seasonal changes in other diarrhoea pathogens. In particular, bacterial pathogens in particular are known to peak in summer months. Assuming that each study carried out consistent case identification for all months of the year, rotavirus case count data would be reliable within each particular study. In addition, five further criteria were required for inclusion: (i) study site within 24° north or south of the equator; (ii) monthly data on at least one of the following climatological variables was reported or available from another source: temperature, rainfall or relative humidity; (iii) study location was confined to a geographic area to which a single weather data set would apply (i.e. no country-wide studies); (iv) study was written in either English or Spanish; and (v) study had a surveillance (rather than case-control or cohort) design to minimize variation in approaches to case identification; papers describing the results of case-control studies were only included if the authors reported rotavirus incidence for cases identified through hospital diarrhoea surveillance separately from controls. Cohort studies were excluded. A total of 26 articles fit these criteria and were included in the analysis presented here. Six papers were excluded because of publication language; these papers were not examined so it is unknown whether they met the other inclusion criteria.

All data reported in the published papers was taken directly from tables or extracted from graphs using DigitizeIt software (I Bormann; www.digitizeit.de). Monthly climatological data for each region were taken from the published paper or from online databases of historical climatological data of the US National Climatic Data Center.^{17–19} Latitude, altitude, average yearly temperature and average yearly rainfall (or number of days of rain per year for the study location) were taken from Weatherbase.²⁰

Analysis

To estimate the association of climatological variables and the frequency of rotavirus, univariate generalized log-linear Poisson regression models were carried out for each study location, using monthly data of number of rotavirus cases per month. The inference on the associations was adjusted to account for the possibility of serial dependence of the residuals (a common problem when time-series are compared) by using a Newey regression approach.²¹ A 5-month and 12-month lag in residual auto-correlations was assumed for studies that were carried out for less than or equal to and >15 months, respectively; the resulting statistical inference was not sensitive to assumptions on the correlation lag.

Studies were also combined to get an overall (average) association between monthly rotavirus incidence (count) and mean temperature, mean rainfall and relative humidity using a generalized estimating equation (GEE) approach, controlling for residual (within study) correlation and using a loglinear (Poisson regression) link.²² An auto-regressive (AR1) working correlation model was used, with robust standard errors to protect the inference against misspecification of this model. This approach accounts for correlation stemming from between-study variation as well as serial correlation in monthly data points within studies. Because studies differ in their mean numbers of rotavirus (due both to different incidences as well as different and sometimes unknown denominators) we also included 'study' as a categorical (fixed effect) variable in the model. This can be thought of as stratifying by study and thus assumes studies have different underlying (baseline) mean counts of rotavirus (due in part to having different population sizes), but assumes the association (relative rate for a unit increase) of the climate variables is the same for all studies. If this is not true, the resulting estimate of the single association can be thought of as a weighted average relative rate. Because the climatological variables are highly related to one another, separate analyses were carried out for each.

A random effects model was used for assessing within- and between-study heterogeneity in rotavirus incidence and overall heterogeneity between studies in the association of rotavirus incidence and climatological variables was tested with a meta-analysis function. Covariates including altitude, latitude, average monthly rainfall, average temperature, range in temperature, range in rainfall, duration of study and total number of rotavirus cases reported were explored for patterns that explained residual variability. Specifically, we included multiplicative interaction terms of categorical study*climatological variable and tested the overall significance of this interaction. We examined whether adding other study-specific variables changed the significance of the overall test of study*climatological variable interaction. All statistical analyses were carried out using STATA software.

Results

A total of 26 studies from 15 countries between latitudes 24° S and 24° N were included in the analysis (Table 1). $23-48$ These studies took place between 1975 and 2003, with study duration ranging from 1 to 10 years. In some studies, enrolment was limited to children, and in others all ages were included. However, most of the patients were children because of the predominance of rotavirus disease in infants and young children.

In the univariate analyses, an inverse relationship between monthly rotavirus incidence and climatological variables was consistently found in the data; 65%, 55% and 60% of studies showed a significant negative association with temperature, rainfall and relative humidity, respectively. For the same respective variables, only 10%, 18% and 0% had significant positive correlations.

Table 1 Summary of Studies included in Review Table 1 Summary of Studies included in Review

The pooled results are shown in Table 2. The model can be interpreted as a weighted average of the individual study estimates to produce a pooled measure of association, the incidence rate ratio (IRR), which is simply interpreted literally—the ratio of mean rates in two different populations that differ by a specified change in the exposure. One can also report the relative effect, or 1-IRR, expressed as a percentage change. These models suggest that on average, across all studies analysed, for every 1°C (1.8 8F) increase in mean temperature, the incidence of rotavirus decreases by 10% [IRR = 0.90 (95% CI: 0.87–0.94); P < 0.0001]; for every 1 cm (0.39 in.) increase in mean monthly rainfall, the incidence of rotavirus decreases by 1% [IRR = 0.99 (95% CI: 0.99–1.00); $P = 0.001$]; and for every 1% increase in relative humidity, the incidence of rotavirus decreases by 3% [IRR = 0.97 (95% CI: 0.95–1.00); $P = 0.018$]. For the median values for the studies of mean temperature $[7^{\circ}C (12.6^{\circ}F)]$, mean monthly rainfall $[31 \text{ cm}]$ (12.2 in.)] and relative humidity (22%) the analysis showed reductions in rotavirus incidence of 51% $[IRR = 0.49 \quad (95\% \quad CI: \quad 0.37-0.65); \quad P < 0.0001],$ 21% [IRR = 0.79 (95% CI: 0.69–0.91); $P = 0.001$], and 44% [IRR = 0.56 (95% CI: 0.34–0.90); $P = 0.018$], respectively.

The meta-analysis revealed significant heterogeneity $(P < 0.0001)$ in studies for all climatological variables assessed. This heterogeneity between studies can be assessed visually in Figure 1, which plots the results of the univariate regression analyses, showing Newey West standard errors. Examining the residual variance of rotavirus incidence in simple random effects models (one for each of the climatological variables of interest) within the random effects (GLS) model, 12–39% of unexplained variation in the model was seen within studies, and 61–88% was seen between studies (Table 2). The most relevant heterogeneity was that for the associations of incidence of rotavirus and climatological variables and this was significant for all the climate variables. When the interaction of these climatological variables and study was assessed (as described in the methods section), none of the covariates explored (altitude, latitude, average monthly rainfall, average temperature, range in temperature, range in rainfall, duration of study and total number of rotavirus cases reported) could explain the between-study heterogeneity seen in the variability of association of climatological variables on the incidence of rotavirus.

Discussion

aData not available for every month.

Data not available for every month.
Significant $(P<0.05)$.

*Significant (P<0.05).

The results of this review suggest that numbers of rotavirus infections tend to be highest under cool, dry conditions in the tropics. Negative associations between monthly rotavirus prevalence and climatological variables analysed predominate in both the univariate and pooled analyses. A total of 23 studies

The log-linear Poisson generalized estimating equation (GEE) model controls for residual (within study) correlation and includes study as a categorical (fixed effect). Both the coefficient and the incidence rate ration (IRR) for a one unit change are shown for the results of the GEE model. The generalized least squares (GLS) Random Effects Model assesses within- and between-study variability.

(89%) showed an inverse correlation with at least one climatological variable (18 studies, or 69% statistically significant), compared with 10 (39%) showing a positive correlation (six studies, or 23% statistically significant) with at least one climatological variable (Table 1). According to the pooled GEE analysis, low values of all climatological variables predicted increased monthly incidence of rotavirus disease in patients with gastroenteritis.

Using data on the total number of monthly rotavirus cases, rather than proportion of diarrhoea patients testing positive for rotavirus, avoided the potential for reporting on patterns driven by seasonal changes in other diarrhoea pathogens. However, we should note that similar results were found with both approaches (total case count and proportion of diarrhoea cases testing positive for rotavirus).

The effect of seasonal changes on rotavirus incidence seen here is not as extreme in the tropics as it is in temperate areas of the world. Rotavirus is found year-round in the tropics with peaks and valleys, whereas incidence often goes to zero in some months in temperate areas. One explanation for this phenomenon is that less climatic variability exists in tropical climates and zones, so variations in climatological variables are not large enough to cause the observed effect. Still, the fact that rotavirus persists year-round in tropical areas of the world, and that rotavirus responds to climatic changes in many different climatic zones throughout the world, suggests that it is not an absolute temperature or humidity level that favors rotavirus transmission, but rather a relative change in climatic conditions.

We see a large amount of heterogeneity both within and between studies in the pooled analysis. The significant unexplained variation is a limitation of the study. The heterogeneity suggests that we would expect to see a stronger effect, and therefore have greater predictive power, if we could reduce some of the sources of variation between the different studies reviewed, such as socioeconomic status of patients, age of patients, sampling scheme, diagnostic methods used, lengths of studies, numbers of participants sampled, populations of study regions and differing climatic conditions at each study location. Most studies included only children while others included patients

of all ages. Also, the majority of studies reviewed were carried out for 2 years or less, which is a relatively short period of time to capture the effects of seasonality; studies of longer duration are preferable for establishing the relationship between climate and rotavirus disease. While all studies lie within the latitudes defined as the tropics, various climatic regimes (e.g. rainforest vs semi-arid) prevail in the different settings and at different altitudes, potentially confounding the results. We were unable to account for these differences in our analysis of potential covariates.

Understanding rotavirus transmission

The heterogeneity in effect observed in the pooled analysis is not surprising given that this analysis did not take into account additional factors potentially affecting rotavirus transmission, such as sanitation and hygiene practices or flood peaks. Several authors of the articles reviewed noted multiple peaks in rotavirus incidence as affected by the monsoon rains (Table 1). Flooding in conjunction with poor sanitation could augment the waterborne component of rotavirus transmission, obfuscating the seasonal patterns, which might be driven more by other routes of transmission, such as the air or fomites.

Strong evidence suggests that rotavirus is a waterborne pathogen. The virus can retain its infectivity for several days in aqueous environments, and waterborne spread has been implicated in a number of rotavirus outbreaks.⁷ However, the high rates of infection in the first 3 years of life regardless of sanitary conditions, the failure to document fecal-oral transmission in several outbreaks of rotavirus diarrhoea, and the dramatic spread of rotavirus over large geographic areas in the winter in temperate zones suggests that water alone may not be responsible for all rotavirus transmission.⁵ No direct evidence shows that fomites and environmental surfaces play a role in the spread of rotavirus gastroenteritis, but indirect evidence shows that these possess a strong potential for spreading rotavirus gastroenteritis. Rotaviruses can remain viable on inanimate surfaces for several days when dried from a fecal suspension.

Many authors have also suggested that rotavirus spreads through the air. In nosocomial outbreaks of rotavirus gastroenteritis, many patients show

Figure 1 Heterogeneity plots of incidence rate ratios (IRR), showing 95% confidence intervals using Newey West standard errors, for regressions of rotavirus incidence vs: (A) monthly mean temperature (${}^{\circ}$ C); (B) monthly rainfall (cm); and (C) relative humidity (%). The pooled effect from the generalized estimated equation (GEE) analysis is also shown

symptoms of upper respiratory tract infection before the onset of diarrhoea, although the rotavirus has not been isolated from the respiratory tract.⁷ Other evidence also points to a respiratory mode of spread. For example, large outbreaks have been recorded in both mid-Pacific island groups and Native American reservations where affected population groups were widely separated geographically. In both of these cases, each population had its own water supply and the rotavirus epidemic spread rapidly with little or no contact between the various groups.⁸ In the United States, seasonal rotavirus activity occurs in a sequential manner, beginning first in the Southwest from October through December and ending in the Northeast in April or May.⁴⁹ This pattern of seasonal spread is similar to other respiratory viruses such as influenza and measles.⁸ Bishop proposes that the explanation for these patterns might lie in the airborne spread of aerosolized particles that are ingested, rather than through respiratory tract infections.6

We speculate that the airborne component of rotavirus transmission might be responsible for the seasonal pattern of rotavirus disease. A relative drop in humidity and rainfall combined with drying of soils in higher temperatures might increase the aerial transport of dried, contaminated fecal material (in the form of droplet nuclei), and might also lead to increased formation of dust, which could provide a substrate for the virus particles. Increased burning of organic materials during the dry season may also increase the amount of particulates in the air. Airborne particles could settle out and infect water supplies or environmental surfaces, or could be ingested. Particles carried on fomites such as clothing could also play a role in large-scale dispersal of rotavirus organisms.

Some mechanical force would likely be required for aerosolization to occur, and wind might play this role, as well as help disperse the particles once formed. In a 4-year study of rotavirus in Pune, India, a tight correlation was seen between number of days with easterly wind and the number of rotavirus diarrhoea cases as functions of time.³⁴ Further research on the relationship between wind patterns and rotavirus incidence might shed light on this potential transmission mechanism.

Conclusions

The widely cited conclusion of Cook et al.² that seasonality of rotavirus infections in the tropics is less distinct than in temperate zones was based on a definition of winter as December–March in the northern hemisphere and June–September in the southern hemisphere. The results of this review suggest that local climatological variables provide a better predictor of seasonality in the tropics, where weather patterns differ from those in the temperate zones. This review reveals a trend for rotavirus to occur in the cool, dry seasons in tropical countries, as observed in temperate zones. These results suggest that paying close attention to *local* climatic conditions will improve our understanding of the transmission and epidemiology of rotavirus disease.

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KEY MESSAGES

- Incidence of rotavirus disease responds to changes in climate in the tropics, with the highest number of infections found at the colder and drier times of the year.
- Monthly rotavirus incidence is significantly negatively correlated with temperature, rainfall, and relative humidity in the majority of studies reviewed.
- Rotavirus previously was not thought to respond to seasonal changes in tropical regions of the world.

References

- ¹ Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhoea. Emerg Infect Dis 2006; 12:304–6.
- ² Cook SM, Glass RI, LeBaron CW, Ho MS. Global seasonality of rotavirus infections. Bull World Health Organ 1990;68:171–77.
- ³ Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis 2003;9:565–72.
- 4 Cunliffe NA, Kilgore PE, Bresee JS et al. Epidemiology of rotavirus diarrhoea in Africa: a review to assess the need for rotavirus immunization. Bull World Health Organ 1998; 76:525–37.
- ⁵ Parashar UD, Bresee JS, Gentsch JR, Glass RI. Rotavirus. Emerg Infect Dis 1998;4:561–70.
- ⁶ Bishop RF. Natural history of human rotavirus infection. Arch Virol Suppl 1996;12:119–28.
- ⁷ Ansari SA, Springthorpe VS, Sattar SA. Survival and vehicular spread of human rotaviruses: possible relation to seasonality of outbreaks. Rev Infect Dis 1991;13:448-61.
- ⁸ Haffejee IE. The epidemiology of rotavirus infections: a global perspective. J Pediatr Gastroenterol Nutr 1995; 20:275–86.
- ⁹ Glass RI, Parashar UD. The promise of new rotavirus vaccines. N Engl J Med 2006;354:75-77.
- ¹⁰ Ruiz-Palacios GM, Perez-Schael I, Velazquez FR et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med 2006;354:11–22.
- ¹¹ Vesikari T, Matson DO, Dennehy P et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 2006;354:23-33.
- ¹² Grimwood K, Buttery JP. Clinical update: rotavirus gastroenteritis and its prevention. Lancet 2007;370:303-4.
- ¹³ Glass RI, Bresee JS, Turcios R, Fischer TK, Parashar UD, Steele AD. Rotavirus vaccines: targeting the developing world. *J Infec Dis* 2005;192(Suppl 1):S160-66.
- ¹⁴ Glass RI, Parashar UD, Bresee JS et al. Rotavirus vaccines: current prospects and future challenges. Lancet 2006; 368:323–32.
- ¹⁵ Glass RI, Bresee J, Jiang B, Parashar U, Yee E, Gentsch J. Rotavirus and rotavirus vaccines. Adv Exp Med Biol 2006;582:45–54.
- ¹⁶ D'Souza RM, Halll G, Becker NG. Climatic factors associated with hospitalizations for rotavirus diarrhoea in children under 5 years of age. Epidemiol Infect 2008;136:56-64.
- ¹⁷ U.S. National Climatic Data Center. Monthly Global Surface Data. [http://cdo.ncdc.noaa.gov/pls/plclimprod/cdomain.](http://cdo.ncdc.noaa.gov/pls/plclimprod/cdomain) DS3500?datasetabbv=DS3500 (November 2005, date last accessed).
- ¹⁸ U.S. National Climatic Data Center. Global Climate Observing System.<http://www.ncdc.noaa.gov/gsn/gsn> (November 2005, date last accessed).
- ¹⁹ U.S. National Climatic Data Center. The Global Historical Climatology Network.<http://lwf.ncdc.noaa.gov/cgi-bin/> res40.pl (November 2005, date last accessed).
- ²⁰ Weatherbase.<http://www.weatherbase.com/> (May 2004, date last accessed).
- ²¹ Newey WK, West KD. A simple, positive, semi-definite, heteroskedasticity and autocorrelation consistent covariance matrix. Econometrica 1987;55:703-8.
- ²² Liang K, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22.
- 23 Unicomb LE, Bingnan F, Rahim Z et al. A one-year survey of rotavirus strains from three locations in Bangladesh. Arch Virol 1993;132:201–8.
- 24 Unicomb LE, Kilgore P, Faruque ASG et al. Anticipating rotavirus vaccines: hospital-based surveillance for rotavirus diarrhoea and estimates of disease burden in Bangladesh. Pediatr Infect Dis J 1997;16:947–51.
- ²⁵ Stoll BJ, Glass RI, Huq MI, Khan MU, Holt JE, Banu H. Surveillance of patients attending a diarrhoeal disease hospital in Bangladesh. Br Med J 1982;285:1185–88.
- ²⁶ Bingnan F, Unicomb LE, Rahim Z et al. Rotavirusassociated diarrhoea in rural Bangladesh: two-year study of incidence and serotype distribution. J Clin Microbiol 1991;29:1359–63.
- ²⁷ Biswas R, Lyon DJ, Nelson EA, Lau D, Lewindon PJ. Aetiology of acute diarrhoea in hospitalized children in Hong Kong. Trop Med Int Health 1996;1:679–83.
- ²⁸ Chan PKS, Tam JS, Nelson EAS et al. Rotavirus infection in Hong Kong: epidemiology and estimates of disease burden. Epidemiol Infect 1998;120:321–25.
- Nelson EAS, Tam JS, Bresee JS et al. Estimates of rotavirus disease burden in Hong Kong: hospital-based surveillance. *J Infec Dis* 2005;195(Suppl 1):S71-79.
- ³⁰ Tam JS, Kum WWS, Lam B, Yeung CY, Ng MH. Molecular epidemiology of human rotavirus infection in children in Hong Kong. J Clin Microbiol 1986;23:660–64.
- ³¹ El Assouli SM, Mohammed KA, Banjar ZM. Human rotavirus genomic RNA electropherotypes in Jeddah, Saudi Arabia from 1988 to 1992. Ann Trop Paediatr 1995;15:45–53.
- ³² Espejo RT, Calderón E, González N, Salomon A, Martuscelli A, Romero P. Presence of two distinct types of rotavirus in infants and young children hospitalized with acute gastroenteritis in Mexico City, 1977. J Infec Dis 1979;139:474–77.
- ³³ Velazquez FR, Luna G, Cedillo R, Torres J, Munoz O. Natural rotavirus infection is not associated to intussusception in Mexican children. Pediatr Infect Dis J 2004;23:S173–78.
- ³⁴ Purohit SG, Kelkar SD, Simha V. Time series analysis of patients with rotavirus diarrhoea in Pune, India. J Diarrhoeal Dis Res 1998;16:74–83.
- ³⁵ Moe K, Shirley JA. The effects of relative humidity and temperature on the survival of human rotavirus in faeces. Arch Virol 1982;72:179–86.
- ³⁶ Brown DW, Mathan MM, Mathew M, Martin R, Beards GM, Mathan VI. Rotavirus epidemiology in Vellore, south India: group, subgroup, serotype, and electrophoretype. J Clin Microbiol 1988;26:2410-14.
- ³⁷ Urquidi V. Molecular epidemiology of human rotavirus infection in Coro, Venezuela. Acta Cient Venez 1989; 40:33–39.
- ³⁸ Viera de Torres B, Mazzali de Ilja R, Esparza J. Epidemiological aspects of rotavirus infection in hospitalized Venezuelan children with gastroenteritis. Am J Trop Med Hyg 1978;27:567–72.
- ³⁹ Hieber JP, Shelton S, Nelson JD, Leon J, Mohs E. Comparison of human rotavirus disease in tropical and temperate settings. Am J Dis Child 1978;132:853-58.
- ⁴⁰ Muhe L, Fredrikzon B, Habte D. Clinical profile of rotavirus enteritis in Ethiopian children. Ethiop Med J 1986;24:1-6.
- ⁴¹ Mutanda LN. Epidemiology of acute gastroenteritis in early childhood in Kenya III> distribution of the aetiological agents. East Afr Med J 1980;57:317-26.
- ⁴² Mutanda LN, Kinoti SN, Gemert W, Lichenga EO. Age distribution and seasonal pattern of rotavirus infection in children in Kenya. J Diarrhoeal Dis Res 1984;2:147–50.
- ⁴³ Suzuki H, Sato T, Kitaoka S et al. Epidemiology of rotavirus in Guayaquil, Ecuador. Am J Trop Med Hyg 1986;35:372–75.
- ⁴⁴ Soenarto Y, Sebodo T, Ridho R et al. Acute diarrhoea and rotavirus infection in newborn babies and children in Yogyakarta, Indonesia, from June 1978 to June 1979. J Clin Microbiol 1981;14:123–29.
- ⁴⁵ Marjoribanks HC, Croxson MC, Potoi N, Bellamy AR. Infantile gastroenteritis in Western Samoa. N Z Med J 1988;101:195–97.
- ⁴⁶ Mpabalwani M, Oshitani H, Kasolo F et al. Rotavirus gastro-enteritis in hospitalized children with acute diarrhoea in Zambia. Ann Trop Paediatr 1995;15:39–43.
- ⁴⁷ Rosa e Silva ML, Naveca FG, Pires de Carvalho I. Epidemiological aspects of rotavirus infections in Minas Gerais, Brazil. Braz J Infect Dis 2001;5:215–22.
- ⁴⁸ Pereira HG, Linhares AC, Candeias JA, Glass RI. National laboratory surveillance of viral agents of gastroenteritis in Brazil. Bull Pan Am Health Organ 1993;27:224–33.
- ⁴⁹ Torok TJ, Kilgore PE, Clarke MJ, Holman RC, Bresee JS, Glass RI. Visualizing geographic and temporal trends in

rotavirus activity in the United States, 1991 to 1996. National respiratory and enteric virus surveillance system collaborating laboratories. Pediatr Infect Dis J 1997;16:941–46.