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Signature:

_____ _____

Sharia M Ahmed Date

The Global Seasonality of Norovirus Gastroenteritis

By

Sharia M Ahmed

Master of Public Health

Global Epidemiology

Karen Levy

Faculty Thesis Advisor

Ben Lopman

Thesis Field Advisor

The Global Seasonality of Norovirus Gastroenteritis

By

Sharia M Ahmed

B.A., University of Minnesota, 2009

B.S., University of Minnesota, 2009

Faculty Thesis Advisor: Karen Levy, PhD, MPH

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Abstract

The Global Seasonality of Norovirus Gastroenteritis

By Sharia M Ahmed

Background: Norovirus is the leading cause of epidemic, acute gastroenteritis in industrialized countries, and may be a cause of severe disease in certain populations (e.g. children, elderly, and hospitalized patients). Norovirus is generally recognized to have an irregular wintertime seasonality in temperate climates, but these patterns have not been systematically described across geographic areas in the era of modern diagnostics.

Methods: We present the results of a systematic review and meta-analysis of norovirus gastroenteritis across various geographic regions. In the systematic review we searched for publications that reported at least one full year of monthly data on norovirus outbreaks or cases in a specified geographic region. The initial literature search identified 287 potential publications, with 78 meeting the inclusion criteria. Data were then extracted from each publication using Plot Digitizer software.

Results: The proportion of cases/outbreaks of norovirus per calendar month was calculated from studies representing twenty-six countries on six continents (37 case-based studies, 32 outbreak-based studies, representing a total of 12 years of data).

Conclusions: There is a clear seasonality of norovirus across the six continents included in this study, with disease burden peaking in winter months in the northern hemisphere.

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INTRODUCTION

Background on Norovirus

Diarrheal disease can usually be attributed to a few specific pathogens, and noroviruses are the most commonly identified cause of gastroenteritis among sporadic cases and outbreaks (1). Within the United States, norovirus is estimated to be the top foodborne pathogen responsible for illness, ranking second in foodborne illness accounting for hospitalization, and is the fourth most frequent cause of death from foodborne disease. This equates to 5.4 million illnesses, 14,000 hospitalizations, and approximately 150 deaths annually attributable to norovirus in the US (2).

Noroviruses are RNA viruses of the family *Caliciviridae* (3), and are classified into one of five genogroups (GI-GV) (4). Norovirus outbreaks frequently occur in healthcare, long-term care, daycares, and school settings (5) in industrialized areas, and are associated with deaths among the elderly (6). In developing areas, children may suffer the worst morbidity and mortality from norovirus due to malnutrition and lack of access to healthcare (7).

Seasonality of Norovirus

Existing published reviews of norovirus cover a plethora of topics, including describing norovirus in specific settings (e.g., hospitals in general, intensive care units, nursing homes, cruise ships), estimating the effect of interventions in these settings, exploring the relationship between norovirus and specific blood groups or enzymes, and understanding norovirus in non-human hosts.

A few reviews in particular focus on seasonal aspects of norovirus distribution. Norovirus has long been recognized as having a strong winter seasonality, and was

formerly known as winter vomiting disease (8). Mounts et al. (2000) evaluated data from 1978-1998 from eight countries and showed that norovirus cases occurred year-round, but that a clear peak in incidence occurred in cold months (9).

Another review of norovirus outbreak publications found that "foodservice and winter outbreaks were significantly associated with higher attack rates". The authors note significant associations of specific strains with specific types of outbreaks, with multiple strains usually being associated with waterborne and foodborne outbreaks, waterborne outbreaks being significantly associated with GI strains, and GII being associated with healthcare and winter outbreaks (10).

While the role of genetics in explaining norovirus outbreaks is becoming better and better understood, the role of environmental factors in norovirus outbreaks remains less well documented. Frequent genetic changes of norovirus are important in determining when outbreaks/epidemics occur, with GII.4 being the most common causative agent (11).

In a multi-country study in Europe, Lopman et al. (2004) found that the emergence of new strains of norovirus can be associated with an unusual seasonal pattern as well as overall increase of disease. Specifically, the 2002-2003 season saw an increased number of norovirus outbreaks and an unusual spike in outbreaks in warmer months, concurrent with the emergence of a new GII.4 strain. This new variant may be more virulent or more environmentally stable, contributing to its unusual seasonality (12). The available knowledge regarding environmental factors of norovirus outbreaks is less detailed.

Norovirus can and has been implicated in almost any setting where people are closely gathered. This is not surprising, given that noroviruses have been found not only in feces, but also in vomitus (13). There is also increasing evidence that norovirus can remain viable for long periods in the environment (11).

One international team of researchers found that norovirus was regularly found on produce, though sequence confirmation was often not successful. In general, they discuss how an increasing number of norovirus outbreaks are associated to fresh produce (14). If the availability of fresh produce is less and less contingent on real-time meteorological variables, this could have important implications for the effectiveness of meteorological data serving as predictors of the seasonality of norovirus.

Seasonality of Infectious Diseases

There is a growing body of literature describing the seasonality of infectious diseases. It is well documented that certain diseases often peak during a given season and at a characteristic strength and duration every year. This is not to say, however, that the disease is not present in the off-season, just at a much lower strength and often only as sporadic cases rather than epidemics. When epidemics do occur, it is often simultaneously in geographically disparate locations. Latitude is often an important predictor of when and how strong spikes in disease activity occur (15).

For example, influenza and rotavirus have well-established winter peaks, while polio peaks in the summer. This influenza peak usually only varies by 5-10 weeks from year to year, and peaks with greater strength as one gets farther from the equator. Epidemic meningococcus is rare in the off-season, even though there is no decrease in carriage during this time (15). When studying all-cause mortality in a given location,

distinct seasons of greater mortality have been observed. A shift in these well-established mortality seasons can be indicative of social and infrastructural changes (16).

The mechanisms by which these seasonal descriptors actually influence disease are varied. Temperature, precipitation, and availability of resources are all important actors on population dynamics. This is because these environmental predictors mediate host behaviour, contact rates, pathogen viability in the environment, changes in host immune defense, and seasonality of host births and deaths (17).

A number of studies have looked at the seasonality of diarrheal disease specifically. In Taiwan, maximum temperature and extreme rainfall days have been found to be strongly related to diarrhea morbidity. Monthly average temperature, total rainfall, and monthly average humidity were also explored, but not found to be as important of predictors of monthly diarrheal disease (18). A recent study in Thailand found "a strong association between daily mean temperature and precipitation and the incidence of hospitalization due to acute diarrhea…" (19). Significantly, it was also found that population density and GDP modified the effect of weather predictors on diarrhea morbidity, dampening the effect in wealthy, urban populations (19).

An international study of campylobacter explored weather descriptors as predictors of laboratory-confirmed cases. All countries included in the study showed a clear seasonality of campylobacter, with a peak usually occurring in the spring, and generally peaking earlier in countries with warmer winters. However, temperature was not shown to have a strong effect on the outcome, either at a short weather timescale or a seasonal timescale. Also, rainfall was not found to have any effect on campylobacter infection (20).

Rotavirus is perhaps the most well-known and studied of the seasonal diarrheal diseases. In a 2009 study in England, Wales and the Netherlands, researchers found no effect of rainfall and humidity on rotavirus infection, but did find a 13% decrease in reported rotavirus cases per 1°C increase in temperature above a 5°C threshold (21). A study in Bangladesh examined the effect of river level, humidity, and temperature on hospital visits for rotavirus. In their data, rotavirus increased by 5.5% per 10cm rise in the river, decreased as relative humidity increased, and increased 40.2% for each 1°C increase above 29°C (22).

The geographic trends of rotavirus have been described in more detail within the United States. The winter rotavirus season typically begins in December or January in the Southwest, moves up and across the country, and ends in April or May in the Northeast. It is important to note that for the study period of these findings (1997-2004), there was no observable effect of rotavirus vaccine. Also, the El Niño phenomena in 1997 to 1998, as well as the La Niña phenomena from 1998 to 2001, were not found to affect this yearly seasonal-temporal pattern of rotavirus in the US (23).

A systematic review and meta-analysis of rotavirus in tropical settings found a 10% decrease in rotavirus incidence for each 1°C increase in mean temperature, a 1% decrease in rotavirus for each 1cm increase in monthly rainfall, and a 3% decrease in rotavirus for each 1% increase in relative humidity. It is important to note that while rotavirus incidence is less variable in the tropics, compared to temperature climates where incidence can go to zero in the off-season, tropical rotavirus incidence is still responding to climatic descriptors (24). This further adds evidence to the overall hypothesis that weather variables serve as significant predictors of rotavirus activity.

Finally, it should be noted that extreme, unusual (climatic) events can also have a significant influence on the seasonal patterns of disease. In a study examining pediatric diarrhea-associated hospital admissions in Peru, 6,225 excess admissions were attributed to the sustained increased temperature associated with El Niño. For every 1°C increase in temperature, diarrhea admissions increased 8%. This effect was greatest during winter months (25). In a study of the viral load of a flooded river in Germany in 2002, a strong association was found between water temperature and detection of viral genome. However, increased transmission of viral disease was not observed in the flooded area (26), though this could be more indicative of the strong water treatment infrastructure of Germany, rather than a lack of increased risk itself.

Climate Change and Infectious Disease

Researchers are interested in understanding the relationship between climate predictors and infectious disease in order to be able to anticipate how global climate change will affect the epidemiology of infectious diseases. Climate change involves changes in rainfall patterns, surface and air temperatures, and winds and ocean currents at the local, regional, or global level (27). Global warming, a more specific description of climate change, has already been observed in the past century, with a 0.3-0.6°C global increase in temperature. The rate of this temperature increase is expected to accelerate in this century. This increase in global air temperature is and will continue to have an unknown effect on precipitation and soil moisture, which are intricately connected with agriculture and food security. Sea levels are also expected to continue rising at an accelerating rate, which disproportionately affects coastal communities (28).

These global shifts have and will continue to have an impact on human resources, behaviour, and health. Vector habitats change, which will affect vector-borne disease trends. Food and economic stress will impact community-level human immunity, as well as migration patterns. Basic resources such as safe water and sanitation are becoming increasingly difficult to support as the environment changes more and more quickly (28).

All of these will have an impact on infectious disease. For norovirus specifically, climate change is predicted to impact the seasonality of norovirus by influencing the following: transmission, host susceptibility, and the resistance of norovirus to environmental conditions (27).

A study focusing on specific climate variables as independent predictors of norovirus found that cooler temperatures, lower relative humidity, low population immunity, and the emergence of new variants were all associated with increased norovirus activity in England and Wales. Of these predictors, changes in temperature had the greatest attributable risk (29).

Based on studies that indicate a peak of norovirus outbreaks in the winter in northern climates, and in the summer in southern climates, Marshall and Bruggink (2011) concluded in their 2011 review that norovirus outbreak seasonality is not linked to temperature. They point to evidence of waterborne transmission as an indication that rainfall may be a more important predictor of norovirus outbreaks (11).

Rohayem (2009) suggests that due to the virulent nature of norovirus vomitus, increased humidity might be an important factor in norovirus transmission. He also observes that lower water temperatures are associated with increased norovirus activity. Human behaviour, specifically crowding, has often been used to explain increased

incidence of norovirus in colder months. This is even more plausible by considering the seasonal variation in human immunity that also dips during the winter (27).

Systematic Reviews

Within the medical literature, systematic reviews have become a well-established way to condense information from multiple studies into single, easily accessible pieces that synthesize the available evidence on a topic. Health practitioners increasingly use these synopsizes for making informed decisions (30). The Cochrane Review, part of the Cochrane Collaboration that aims to assist and encourage the use of systematic reviews in healthcare decisions, lists the following as important parts of a systematic review:

- a clearly stated set of objectives with pre-defined eligibility criteria for studies;
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies (31).

By examining trends in outcomes, practitioners can avoid sifting through the sometimes contradictory findings of multiple studies (32). This is often achieved by conducting a meta-analysis of systematic review data. A meta-analysis entails pooling data from multiple studies of the same topic, and re-estimating effect measures in this larger dataset (31).

Motivation for this study

The most recent review of global seasonality of norovirus was published over a decade ago, before PCR diagnostics were widely available. In this paper, we present an updated systematic review describing worldwide seasonality of norovirus in the age of modern diagnostics. Other studies of norovirus seasonality have only looked at specific cities/regions, which are more sensitive to unique local behavioural and environmental determinants of infectious disease. This study takes advantage of an increased body of literature that has developed over the past decade with improvements in norovirus diagnostics to include a much larger number of countries, studies, and subjects. We explore if meteorological factors, the emergence of new strains, GDP, latitude, and demographic characteristics are associated with the strength of the norovirus season and the timing of seasonal peaks.

METHODS

Literature review

We searched PubMed through Endnote X4 to identify articles on Norovirus seasonality using the search terms "norovirus" and each of the following terms: "ambient temperature," "climate," "rain," "relative humidity," "season," and "weather." Abstracts were first screened for relevance by two independent reviewers and then original articles were obtained and reviewed for the inclusion of monthly measure of human norovirus burden for at least one contiguous year from 1997 to 2009. Data were extracted from the final set of articles using Plot Digitizer (SourceForge.net). A detailed protocol describing search methodology is provided in the Appendix.

Studies commonly included two different types of outcomes: case data and outbreak data. Case data generally referred to norovirus positive laboratory samples or individual cases reported to regional/national reporting systems. Outbreak definitions varied between papers, but were also from regional/national reporting systems. Therefore, we divided the dataset into two groups for comparability of reported outcome. Authors were contacted if their published figures/tables were not clear enough for digital extraction, and some datasets were expanded when authors replied with more inclusive data. If authors did not respond, or if the researchers were unable to make the published measure comparable to other studies, the article was excluded (eight excluded). Five relevant articles not identified in the search but known to the authors were added to the data. We were able to successfully extract data from papers in Mandarin Chinese, Portuguese, and Polish by translating relevant portions of papers, in particular graphs and tables.

Methods to summarize data

Several data processing steps were carried out to ensure comparability of data across the different study designs and data presentation formats. For articles presenting data stratified by genotype/genogroup, the monthly counts of cases or outbreaks were summed. If the study reported results as percentages but included the total number of cases/outbreaks, monthly percentage measures were back-calculated to counts. Studies presenting monthly percentages without reporting the total number of cases or outbreaks were excluded. Weekly counts were summed to monthly counts, and only single instances of redundant datasets (i.e., multiple published articles using the same data) were used.

Monthly counts of cases or outbreaks were then normalized, averaged and weighted.

Normalized monthly counts of cases or outbreaks P was calculated as follows:

$$P_{ym} = \frac{C_{ym}}{\sum C} \frac{N}{12}$$

Here P_{ym} is the normalized monthly counts in year y and month m, where C_{ym} is the number of cases/outbreaks in year-month ym and N is the total number of months in the study. Hence the normalized monthly count is the proportion of cases or outbreaks that occur in a given month such that the sum for the entire study period of that article equals 1. It serves as an indicator of norovirus activity in a given month and is allowed to vary across years to account for annual variation.

Normalized yearly averages of cases or outbreaks $\widehat{P_m}$ presents the single year series averages reported in articles or was calculated for multi-year studies as follows:

$$\hat{P}_m = \frac{\sum_y P_m}{N_m}$$

Averages were calculated of normalized data, rather than normalizing averages, to account for studies that do not have multiples of twelve months of data.

Weighted normalized summation of cases or outbreaks was calculated as follows:

$$PW_m = \sum_x P_{ymx} \frac{cases_x}{\sum_x cases}$$

Here PW_m presents a single value for each month in the study period based on the normalized monthly counts for all studies x weighted on the relative size of each study.

Weighted normalized yearly averages of cases or outbreaks $\widehat{PW_m}$ was calculated as follows:

$$\widehat{PW_m} = \sum_x \hat{P}_{mx} \frac{cases_x}{\sum_x cases}$$

This is the same as the weighted normalized summation but uses normalized yearly averages instead of normalized monthly counts. It serves as a global-weighted proportion of cases or outbreaks in month m.

Predictors and independent variables

Independent variables for each study location included latitude (degrees), average winter temperature (°C) (December/January/February or June/July/August depending on hemisphere), peak-to-trough ratio of monthly average temperature (per season year), and average monthly precipitation in the wettest month (cm). These data were obtained for the city in which the study occurred. If less than or equal to three cities were in a single study, values were averaged for those cities. If published data were for greater than three cities or for a regional or country as a whole, data for the largest city (by population) was

used. Country-level data on gross-domestic product (GDP), crude birth rate, population density, and if the given year's observation was a new strain year or not (a season year with a significant genetic shift from previous years, which have been document in the 2002-2003 and 2006-2007 seasons) were also included.

Latitude, temperature, and precipitation data were collected from www.weatherbase.com (33) and the World Meteorological Organization (a member of the UN Development Group) (34). Country-level GDP data was obtained from the International Monetary Fund (IMF) website for each country in the dataset (35). Gross domestic product based on purchasing-power-parity (PPP) per capita GDP was used since in this analysis GDP serves as a proxy for infrastructure and services available for water, sanitation, and healthcare. Values were reported in current 2011 international dollars. Population density was reported in population per square kilometer, and the values included were the average of yearly estimates for 1997-2009 (this study period). Crude birth rate was defined as the "number of births over a given period divided by the person-years lived by the population over that period. It is expressed as number of births per 1,000 population." The crude birth rate value used in this study was the average of the five-year estimates for 1995-2000, 2000-2005, and 2005-2010. Both population density and crude birth rate data were obtained from the United Nations Department of Economic and Social Affairs, Population Division, Population Estimates and Projections Section (36).

Statistical methods

The modeling outcome of interest was norovirus season strength, measured as the peak to mean ratio of normalized monthly proportion norovirus cases or outbreaks for a

given season-year. The log of norovirus season strength was used for modeling purposes, to help meet the normality assumption.

A complex, multilevel mixed linear model was deemed most appropriate for the data. Cases and outbreaks were modeled separately. Scatterplots of the outcome versus each individual predictor except new strain year (already a dichotomous variable) were produced. No predictors were categorized. Initial models assumed correlation at the country, city, and study levels. These models included fixed effects of the four potential exposures (latitude, average winter temperature, summer to winter temperature ratio, and average precipitation in wettest month), the four potential confounders (GDP, crude birth rate, population density, and new strain year), and a one-way interaction between GDP and each of the exposures. Initial models also included a random effect at the cluster level, and a three-tier categorical variable for study size.

In a secondary, simplified analysis, multiple years of data were averaged within each small study to get a one-year average of norovirus season strength for that study type and setting. Years were defined by season year (July of a given year to June of the subsequent year). Levels, correlation, and weighting were ignored for this linear regression.

No IRB was necessary for this study as it did not involve research with human subjects.

RESULTS

Our original search yielded 458 articles, 171 of which were duplicates, and 149 were deemed irrelevant based on their title/abstract. Of the remaining 138 articles, 28 did not report data, six did not span an entire year, 11 did not report monthly outcomes, and 10 could not be found or translated. Another five articles were added for relevance that had not been identified in the original search, other datasets were added/removed based on clarifying correspondence with authors, and multiple articles using the same dataset were condensed into a single dataset. The final dataset included 37 sets of data on cases and 32 sets on outbreaks (see Figure 1).

Scatterplots of the outcome and each continuous covariate showed little variation in all covariates except for GDP (see Figure 2). The full range of outcomes were represented by a very small sub-range of each predictor variable except for GDP. The full range of outcome was represented by the full ranges of GDP, i.e. there was no meaningful pattern between GDP and the outcome. Norovirus exhibited a clear seasonality across the six continents represented in this study (Figure 3), with the peak in winter months and a trough in summer months. The appearance of this trend was dampened when moving from North to South, which was expected if colder temperatures or a more severe winter-summer temperature difference is significant in predicting norovirus seasonality. Notable exceptions were the Widdowson et al. (2004) study and the Verhoef et al. (2008) study. Both of these described the seasonality of norovirus outbreaks on cruise ships in the US and Europe respectively, so it is reasonable for these outbreaks to follow the seasonality of cruises (i.e. the overarching risk) rather than meteorological characteristics.

Another unusual finding is the pattern of the Georgiadis et al. 2010 study, which took place in Brazil. Since the meteorological seasonality of Brazil is opposite to the rest of the

included studies, it was expected that Brazil would exhibit a dip in norovirus activity in November-March, the months of highest temperature. This is what was observed in the Victoria et al. 2007 study (also in Brazil). However, the Georgiadis et al. study did not display this clear pattern, reaching the highest peak in norovirus activity in November. These findings should also be compared to the other southern hemisphere studies. The four Australian datasets all roughly exhibited the expected November-March dip in norovirus activity, though the usual seasonal pattern was not as pronounced or distinct as in other studies.

Figure 4, showing the average seasonality across all studies, also supported this clear winter-peak seasonality of norovirus. In the 12 year span of this study, eight years of case data peaked in December-February (winter), with one peaking in November and three peaking in March, while ten years of outbreak data peaked in December-February, with one peaking in March (season 2008-09 is omitted in this graph due to lack of data covering this entire period) (see Figure 4). Studies reporting outbreaks did not appear to peak as sharply as studies reporting cases.

Case studies and outbreak studies showed a distinctly earlier peak of proportion of norovirus cases by month in new strain year 2002-03 (blue), but not in new strain year 2006-07 (green) (Figure 4). Among outbreak studies, 2006-07 also showed a more sustained peak (Figure 4). The 2002-03 early peak supported previous findings and hypothesis.

Meaningful regression models were not able to be estimated for either the full dataset or the simplified dataset. In the full multilevel model, too much collinearity existed among the predictor variables, and did not allow the model to stably converge. Collinearity was not a problem for the simplified dataset, but the regression still could not converge (due to infinite

likelihoods being reached), or the estimates were not significant. See Appendix for non-significant results.

DISCUSSION

These data exhibited a clear seasonality of norovirus, with a peak in the proportion of norovirus burden in winter months. Excluding cruise ship data, 16 out of 37 studies of cases and 19 out of 30 outbreak studies peaked during winter months (December-February in the Northern hemisphere, June-August in the Southern hemisphere). In Europe, where there was more data over a range of years and climates, the relative strength of the norovirus burden peak was clearly during winter months. Georgiadis et al.'s study from Brazil, which failed to show a winter peak in the southern hemisphere, only included data from the 2006-07 season year, a new strain year that is suspected to exhibit unusual seasonality. The study from Victoria et al., also from Brazil and not including data from new-strain years, exhibited the expected wintertime seasonality of norovirus.

In general, outbreak studies exhibited weaker seasonality than case studies. This difference most likely stemmed from having a broader catchment area in outbreak studies, which exerted a smoothing influence and further supplies robustness to the described seasonality.

Based on previous literature (Lopman et al., 2004) we expected to see earlier peaks in new strain years. This was observed for 2002-03 in both cases and outbreaks but not in 2006-07. In fact, the yearly average proportions from Figure 4 shows a late peak for the 2006-07 season in outbreak studies. A late peak could imply that the new strain emerged later in the season year, and therefore may still have peaked faster than expected, but appeared later in the usual season year. Alternatively, this strain may just be less transmissible than other strains. It is also possible that whatever environmental and behavioural factors that time/temperature serve as proxy for were different in the 2006-07 season. A possible example would be less travel compared to other years and therefore slower spread of the new strain.

Overall, the analysis was strongly supportive of a wintertime seasonality of norovirus and provided an updated review of global seasonal trends. As evidenced by the scatterplots in Figure 2, the available data tended to fall within a very limited range of each predictor's potential range. This limited variability of predictive data did not allow regression modeling. Still, the systematic and extensive literature search that informed the descriptive analysis allowed us to be confident in the findings we were able to describe. Using monthly averages of meteorological characteristics, instead of records of the actual meteorological conditions in that location at that time, may oversimplify the data, as well as be too repetitive and therefore correlated across years. Also, it may simply be inappropriate to use monthly averages of weather conditions that impact environmental survival and host behaviour on a continuous basis. Furthermore, country-level demographic descriptors may also be too broad to capture the influence of such demographics at the local level.

These findings were consistent with the existing literature, that norovirus incidence peaks in the winter months in the northern hemisphere. It is less clear when the peak occurs in the southern hemisphere. In their 2011 review, Marshall and Bruggink claim that norovirus incidence peaks in the winter in the northern hemisphere, but in warmer months in the southern hemisphere. This is based on data solely from Australia. While the data from Australia included in this study do not consistently show a wintertime seasonality, they also do not show a consistent summertime seasonality for norovirus. The southern hemisphere data currently available for norovirus seasonality are almost exclusively from Australia, some from Brazil. With the exception of a very small study in Madagascar (n=14), there is no other data from the southern hemisphere. While it is probable that temperature alone is not the only driver of norovirus seasonality, it cannot be concluded from data from Australia alone that norovirus

exhibits a summertime seasonality in the southern hemisphere. Australia is more similar to Europe and northern American countries with regards to behaviour, demographics, as well as business. The reported spike in norovirus incidence in Australia in December through February could also reflect mass importation of the virus from other developed countries when those northern hemisphere nations are peaking in their norovirus burden.

Whether or not the southern hemisphere norovirus burden peaks in the winter months, it was clear that norovirus in the northern hemisphere does peak in the winter. These northern hemisphere findings were consistent enough to inform public health efforts that would be most efficiently implemented at times of critical norovirus risk. Containing transmission of norovirus is key to limiting its burden, and behavioural and technical interventions should be reinforced as winter approaches.

It is still unclear what the seasonality of norovirus is in the southern hemisphere. However, some aspect of winter does seem to drive norovirus transmission in the northern hemisphere. If more detailed predictive data were obtained, specifically more location and year specific meteorological data, the resulting regression models could be very informative in determining what aspects of winter are important predictors of norovirus seasonality. These data are available through the US National Climatic Data Center, and will be utilized in the near future.

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Table 1: Summary of Studies Included in Review

Author	Year_Pub	Ref	Continent	Country	City	Season-Years	Outcome	Latitude (degree)	Avg. Winter Temp (°C)	Summer/ Winter Temp (°C)	Avg rain in wettest month (cm)	New Strain Year (Y/N)	Crude Birth Rate (births per 1,000 pop.)	Pop. Density (pop. per sq. km.)	GDP (PPP per capita)	# Cases/ Outbreaks
Anestad-Vainio		(37, 38)	Europe	Norway	NA	01-08	Cases	59	-3	-5	9	N	12.8	11.9	53376	5274
Beersma	2009	(39)	Europe	Netherlands	Rotterdam	03-07 cases, 03-07 outbreaks	Outbreaks	51	4	5	8.9	N	12.1	388	42331	224 cases, 559 outbreaks
Belliot	2010	(40)	Europe	France	NA	08-09	Outbreaks	48	4	5	6.5	N	12.8	109.2	35049	238
Blanton	2006	(41)	N America	USA	NA	00-04	Outbreaks	NA	NA	NA	NA	N	14.1	30.2	48147	180
Bruggink	2010	(42)	Australia	Australia	Victoria	02-07	Outbreaks	-37	10	2	6	Y	13.3	2.6	40836	767
Buesa	2008	(43)	Europe	Spain	Catalonia, Valencia	01-07	Outbreaks	40	6	4	6.4	N	10.2	83.5	30622	194
Chan_It	2011	(44)	Asia	Japan	Tokyo, Sapporo, Saga, Osaka, Maizuru	07-09	Cases	34	6	7	20.1	N	9	333.6	34362	254
Chhabra	2009	(45)	Asia	India	Pune, Nagpur, Aurangabad	05-07	Cases	19.3	21	2	23	N	25	336.2	3703	89
Dai	2011	(46)	Asia	China	Jiangmen City	06-07	Cases	22	15	2	48.3	N	14	134.5	8394	115
Deng	2009	(47)	Asia	China	Beijing	Avg	Cases	39	-2	-8	22.4	NA	14	134.5	8394	79
Dey	2007	(48)	Asia	Bangladesh	Dhaka	04-05	Cases	23	21	2	39.9	N	25.3	942.7	1697	41
Dey	2011	(49)	Asia	Japan	Maizuru, Tokyo, Sapporo, Saga, Osaka	06-07	Cases	34	6	7	20.1	Y	9	333.6	34362	98
Doyle	2009	(50)	N America	USA	Florida	06-07	Outbreaks	30	13	2	19.6	Y	14.1	30.2	48147	113
Fang	2007	(51)	Asia	China	13 regions listed	Avg	Cases	NA	NA	NA	NA	NA	14	134.5	8394	777
Georgiadis	2010	(52)	S America	Brazil	NA	06-07	Cases	NA	NA	NA	NA	N	19.2	21.3	11846	48
Greer	2009	(53)	N America	Canada	Toronto	06-08	Outbreaks	43	-5	-3	8.1	Y	11.1	3.2	40458	247
Hansman	2004	(54)	Asia	Vietnam	Ho Chi Minh	99-00	Cases	10	27	1	34.3	N	17.8	245.5	3355	1368
Huh	2009	(55)	Asia	S Korea	Gyeonggi province	Avg	Cases	37	-1	-12	34.8	NA	11.3	468.4	31754	367
Hulth	2010	(56)	Europe	Sweden	NA	05-09	Cases	59	-3	-5	7.2	N	11	20	40614	22895
Iritani	2002	(57)	Asia	Japan	Osaka City	97-00	Outbreaks	34	6	7	20.1	N	9	333.6	34362	62
Iritani	2003	(58)	Asia	Japan	Osaka City	97-00	Cases	34	6	7	20.1	N	9	333.6	34362	93
Iritani	2010	(59)	Asia	Japan	Osaka City	06-07	Outbreaks	34	6	7	20.1	Y	9	333.6	34362	144
Johansen	2008	(60)	Europe	Sweden	NA	97-06	Cases	59	-3	-5	7.2	N	11	20	40614	4081
Kelly	2008	(61)	Europe	Ireland	NA	04-05	Outbreaks	53	6	3	7.6	N	15.4	57.2	39508	263
Kirk	2010	(62)	Australia	Australia	Long-term care facilities	02-08	Outbreaks	-33	12	2	13.2	Y	13.3	2.6	40836	1147

Kroneman	2006	(63)	Europe	NA	NA	04-07	Outbreaks	NA	NA	NA	NA	N	NA	NA	NA	952
Kroneman	2008	(64)	Europe	NA	NA	01-06	Outbreaks	NA	NA	NA	NA	N	NA	NA	NA	1643
Lee	2008	(65)	N America	Canada	Alberta	03-04 cases, 03-04 outbreaks	Cases, Outbreaks	51	-7	-2	8.1	N	11.1	3.2	40458	141 cases, 78 outbreaks
Lindell	2005	(66)	Europe	Sweden	mostly Stockholm	01-03	Cases	59	-3	-5	7.2	N	11	20	40614	878
Lopman	2004	(12)	Europe	Denmark	NA	98-03	Cases	55	1	33	7.4	N	12.1	125.1	37742	1896
Lopman	2004	(12)	Europe	Finland	NA	98-03	Cases	60	-5	-3	7.4	N	11.2	15.4	36723	1629
Lopman	2004	(12)	Europe	Germany	NA	99-03	Outbreaks	52	0	-33	6.9	N	8.9	230.9	37936	376
Lopman	2004	(12)	Europe	Hungary	NA	99-03	Outbreaks	47	1	-37	6.3	N	9.7	109	19647	184
Lopman	2004	(12)	Europe	Netherlands	NA	97-03	Outbreaks	52	4	6	10.4	N	12.1	388	42331	270
Lopman	2004	(12)	Europe	Slovenia	NA	00-03	Cases	46	0	-18	15.4	N	9.3	98.6	29179	808
Lopman	2004	(12)	Europe	Spain	NA	99-03	Outbreaks	40	6	4	6.4	N	10.2	83.5	30622	245
Lopman	2004	(12)	Europe	Sweden	NA	97-03 cases, 01-02 outbreaks	Outbreaks	59	-3	-5	7.2	Y	11	20	40614	3213 cases, 1192 outbreaks
Marshall	2003	(67)	Australia	Australia	Melbourne	98-99	Cases	-37	10	2	6	N	13.3	2.6	40836	79
Marshall	2005	(68)	Australia	Australia	Victoria	00-01	Outbreaks	-37	10	2	6	N	13.3	2.6	40836	30
Maunula	2005	(69)	Europe	Finland	Helsinki	98-03	Outbreaks	60	-5	-3	7.4	N	11.2	15.4	36723	252
Medici	2004	(70)	Europe	Italy	Parma	00-03	Cases	44	1	46	9.7	N	9.3	193	30166	63
Napiow…	2010	(71)	Europe	Poland	NA	Avg	Cases, Outbreaks	52	-1	-11	7.6	NA	10.1	118.3	20137	2724 cases, 130 outbreaks
Nataraju	2011	(72)	Asia	India	Kolkata	08-09	Cases	22	21	2	33.3	N	25	336.2	3703	78
Nguyen	2007	(73)	Asia	Vietnam	Ho Chi Minh	02-03	Cases	10	27	1	34.3	N	17.8	245.5	3355	1402
Nguyen	2008	(74)	Asia	Vietnam	Ho Chi Minh	05-06	Cases	10	27	1	34.3	Y	17.8	245.5	3355	32
Onishi	2008	(75)	Asia	Japan	Soma	02-03	Cases	36	5	6	18	Y	9	333.6	34362	105
Papaventsis	2007	(76)	Africa	Madagascar	Antananarivo	04-05	Cases	-18	16	1	29	N	39.3	28.8	943	14
Park	2010	(77)	Asia	S Korea	5 hosp in 3 areas (Seoul, Gyenogsi-do state, Gwangwon-do state)	07-09	Cases	37	-1	-12	34.8	N	11.3	468.4	31754	1169
Puustinen	2011	(78)	Europe	Finland	NA	98-04	Cases	60	-5	-3	7.4	N	11.2	15.4	36723	765
Reuter	2008	(79)	Europe	Hungary	NA	01-07	Outbreaks	47	1	-37	6.3	N	9.7	109	19647	301
Sakon	2007	(80)	Asia	Japan	Osaka City	05-07	Outbreaks	34	6	7	20.1	N	9	333.6	34362	525
Siebenga	2007	(81)	Europe	Netherlands	NA	97-06	Outbreaks	34	6	7	20.1	N	12.1	388	42331	605

Sumi	2005	(82)	Asia	Japan	NA	01-04	Cases	34	6	7	20.1	N	9	333.6	34362	3413
Terletskaia-Ladwig	2011	(83)	Europe	Germany	Baden-Württemberg,	02-09	Cases	52	0	-33	6.9	Y	8.9	230.9	37936	682562
Tu	2007	(84)	Australia	Australia	New South Wales	04-07	Outbreaks	-33	12	2	13	Y	13.3	2.6	40836	734
UK Data[1]	2003/ 2009	(5),(29)	Europe	England/ Wales	NA	97-09 cases, 97-09 outbreaks	Outbreaks	51	4	4	7.9	N	12	246	35974	47109 cases, 4148 outbreaks
Vainio	2006	(38)	Europe	Norway	NA	01-06	Outbreaks	59	-3	-5	9	N	12.8	11.9	53376	197
vanAsten	2011	(85)	Europe	Netherlands	NA	99-07	Outbreaks	52	4	6	10.4	N	12.1	388	42331	746
Verhoef	2008	(86)	Europe	NA	NA	02-07	Outbreaks	NA	NA	NA	NA	Y	NA	NA	NA	29
Victoria	2007	(87)	S America	Brazil	Rio de Janeiro	03-04	Cases	-22	23	1	13.7	N	19.2	21.3	11846	65
Widdowson	2004	(88)	N America	USA	cruiseships	01-02	Outbreaks	NA	NA	NA	NA	Y	14.1	30.2	48147	44
Wilhelm	2010	(89)	N America	USA	Charleston	06-07	Cases	38	2	22	13.2	N	14.1	30.2	48147	979
Yoon	2008	(90)	Asia	S Korea	NA	05-06	Cases	37	-1	-12	34.8	Y	11.3	468.4	31754	114

[1] Special thanks to John Harris for supplying the full series of data.

FIGURES

Figure 1: Flow chart of search

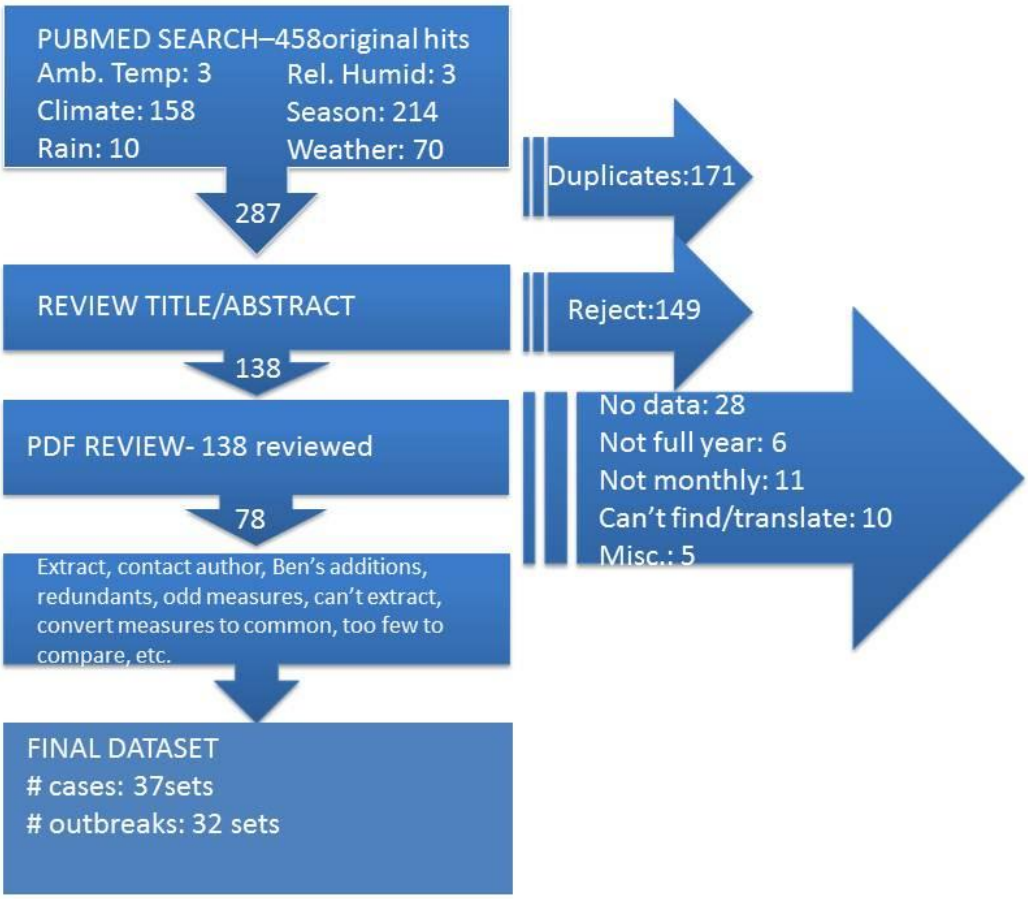


Figure 2: Scatterplots of each predictor against log indicator of norovirus seasonality

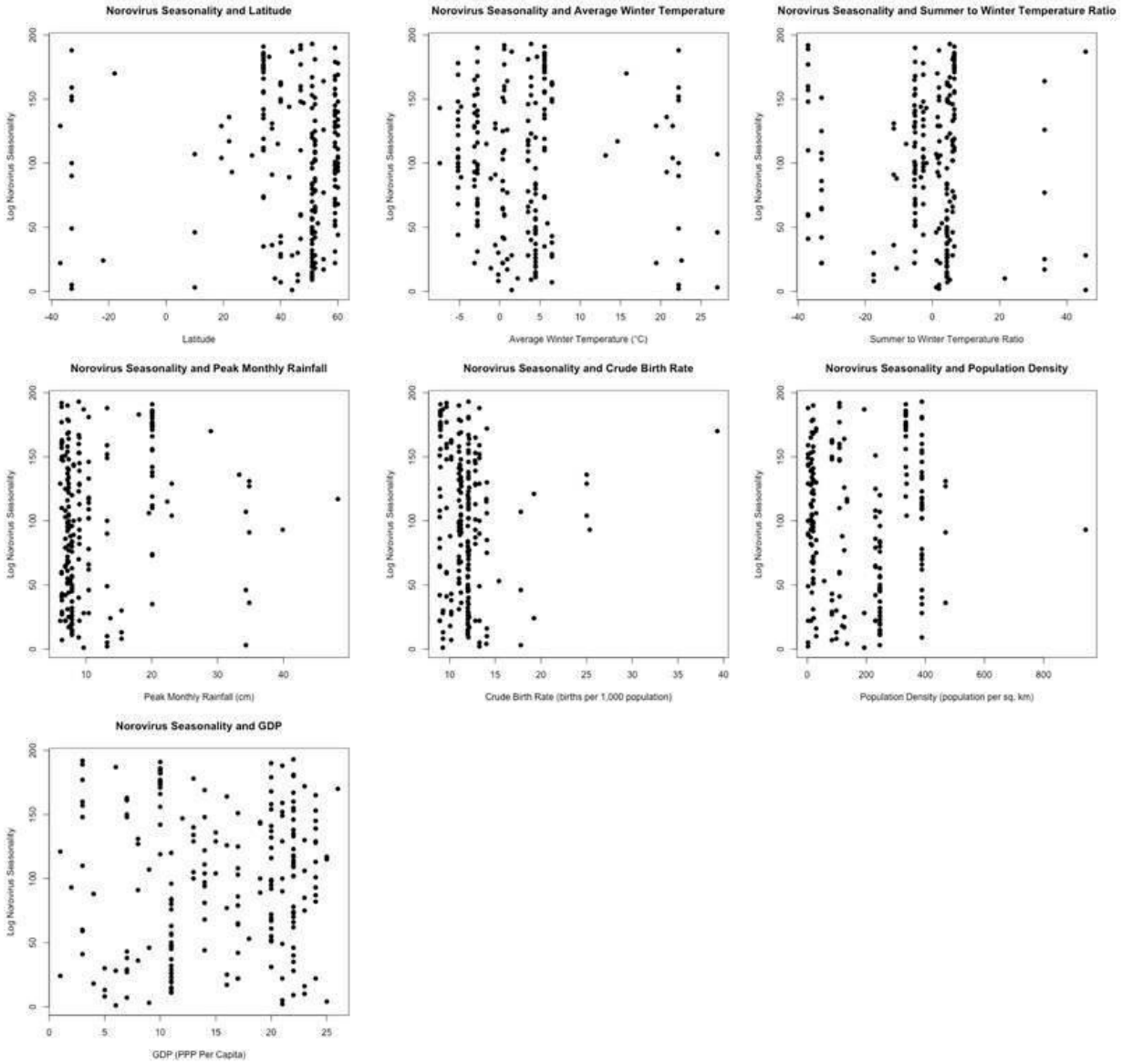
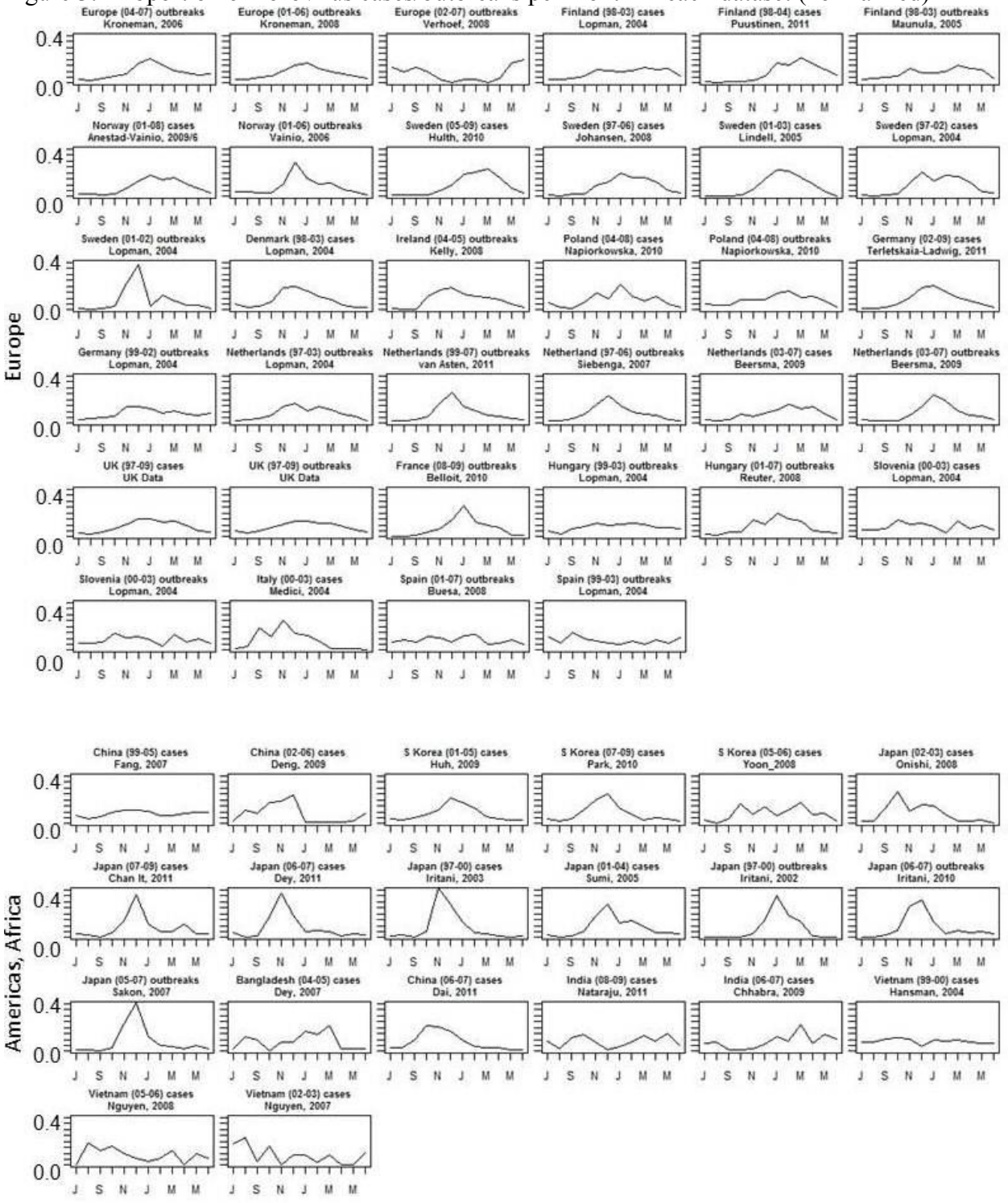


Figure 3: Proportion of norovirus cases/outbreaks per month in each dataset (normalized)



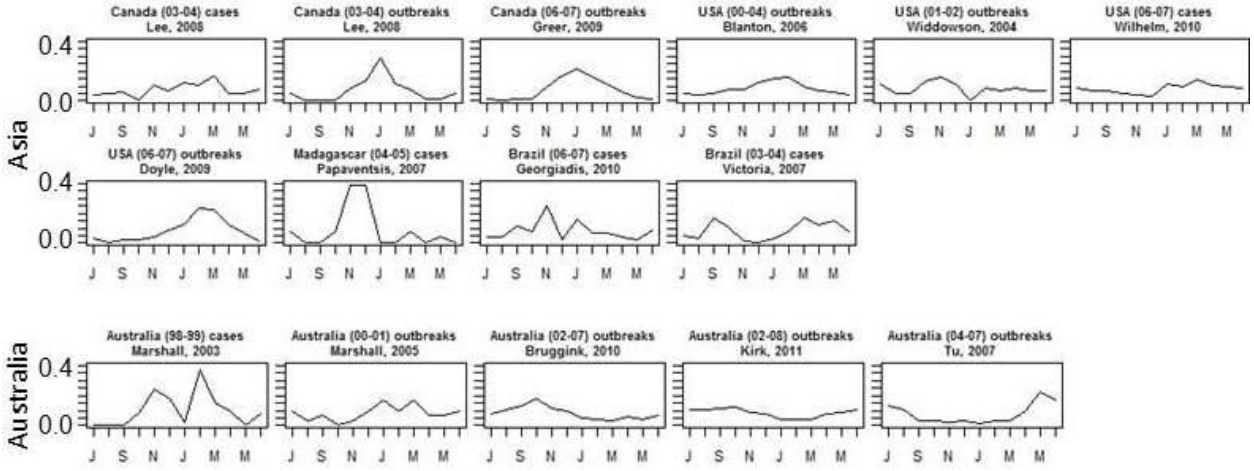
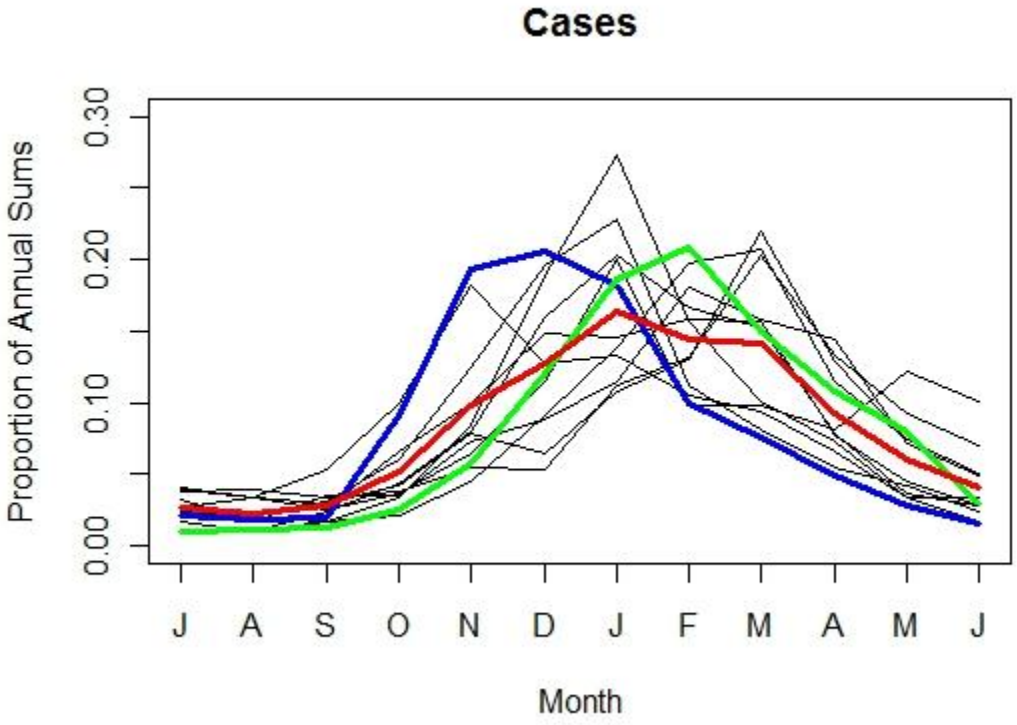
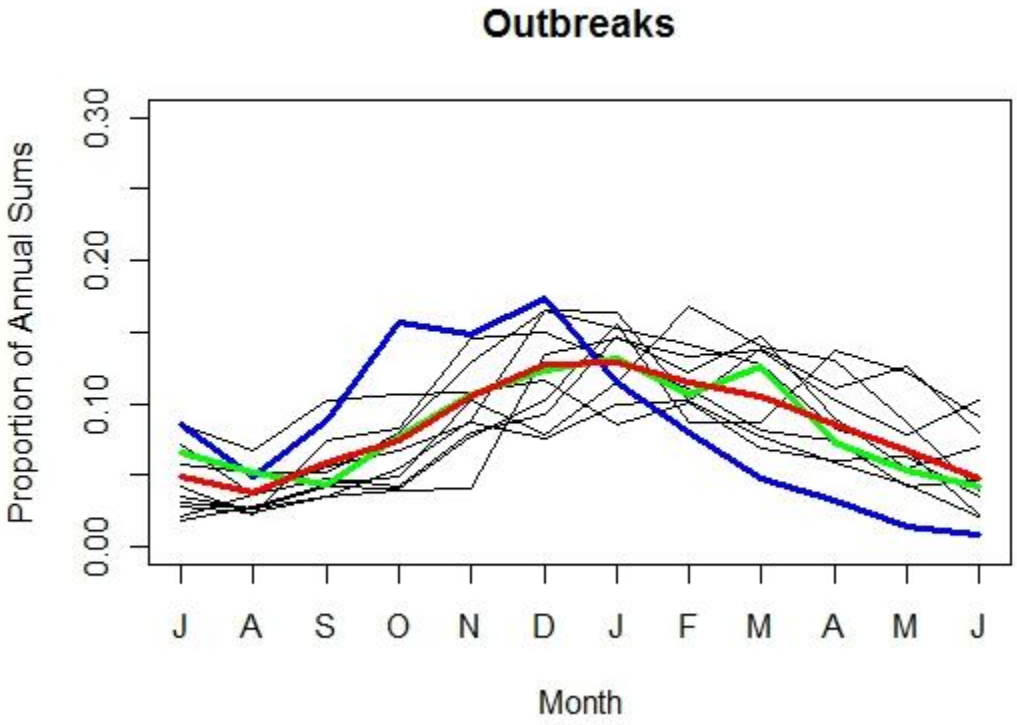

Asia
Canada (03-04) cases
Lee, 2008
Canada (03-04) outbreaks
Lee, 2008
Canada (06-07) outbreaks
Greer, 2009
USA (00-04) outbreaks
Blanton, 2006
USA (01-02) outbreaks
Widdowson, 2004
USA (06-07) cases
Wilhelm, 2010
USA (06-07) outbreaks
Doyle, 2009
Madagascar (04-05) cases
Papaventsis, 2007
Brazil (06-07) cases
Georgiadis, 2010
Brazil (03-04) cases
Victoria, 2007
Australia
Australia (98-99) cases
Marshall, 2003
Australia (00-01) outbreaks
Marshall, 2005
Australia (02-07) outbreaks
Bruggink, 2010
Australia (02-08) outbreaks
Kirk, 2011
Australia (04-07) outbreaks
Tu, 2007
0.4
0.0
J S N J M M

Figure 4: Proportion of norovirus cases/outbreaks by season-year, with new strain years highlighted (Blue=2002-03 Green=2006-07 Red=average)





APPENDIX
Detailed Search Protocol

Creating the Complete ("No Deletes") Pathogen Library

1) Go into EndNote > File > Save As > Title "[Pathogen]_No_Deletes" > Hit Enter
2) Right-click on "My Groups" on left-hand side >Create Group > Title "[Climate-Related Term]." Create a group for each of these terms.
    a) Climate-related term list:
        i) Season
        ii) Rain
        iii) Ambient Temperature
        iv) Relative Humidity
        v) Climate
        vi) Weather
3) Got to File > New > Save As > Title "[Pathogen]_IPS" > Hit Enter
4) In this new library, right-click on "My Groups" on left-hand side >Create Group > Title "[Climate-Related Term]." Create a group for each of these terms.
    a) Climate-related term list:
        i) Incidence
        ii) Prevalence
        iii) Surveillance
5) Go back to the "[Pathogen]_No_Deletes" library.
6) Under the "Online Search" set, click "PubMed (NLM)"
7) Click on the "Search" tab in the bottom half of the screen, then type in [pathogen] and [climate-related term]
    a) Search "Any Field" for [pathogen] and [climate-related term]. Confirm Online Search by clicking "OK."
8) Click on the "Unfiled" group at the top of the left column. Highlight all references and drag into the [climate-related term] group. Note date, time, and number of hits for each search.
9) Repeat for each climate-related term
10) Go to the other library, "[Pathogen]_IPS" and repeat this process for those climate-related terms (steps 3-4).
11) Click on "All References" at the top of the left column. Go to References > Find duplicates > press CANCEL > all duplicates will be highlighted > right-click and move duplicate references to Trash. Note number of duplicates and number of "All References" after deleting duplicates.
12) After deleting duplicate > Right-click on trash > Empty Trash
13) Repeat for "[Pathogen]_IPS" library

To re-run search
Create new library, rerun all terms
Delete duplicates
Create another new library. Add all articles from original search (not including duplicates). Add all articles from new search (not including duplicates). Find duplicates. Delete highlighted duplicates. Delete all articles from duplicates folder. This gets rid of all articles that are counted in both libraries. This leaves only articles that are found in one library (search) and not the other

Creating the ("Deletes") Library

1) Go to the "[Pathogen]_No_Deletes" library. File > Save As > title "[Pathogen]_Deletes"
2) Click on "My Groups" on the left-hand side > Create New Group Set > title "Delections"
3) Right-click on "Deletions" > Create New Group > title "Based on Time"
4) Repeat step 3, title "Based on Title/Abstract"
5) Begin excluding irrelevant references from the main library based on examining titles and abstracts ONLY at this point
    a) Reject based on Title/Abstract if the subject matter is not appropriate (ex. Is a study on oysters)
    b) Reject based on Time if study period is not:
        i) One full year of data (12 months)
        ii) Reports weekly or monthly incidence of diarrheal disease (outbreak)/pathogen incidence
6) Click and drag each reference that is being excluded into the appropriate group based on the reason for exclusion. The original reference in the _____ group must then be "cut" right click to remove from that group

Creating the Combined Library

1) File > New > Library. Then File > Save As > "[Pathogen]_Combined"
2) On the left-hand side Create New Group Set > title "Final Selections"
3) Right-click on "Final Selections" > Create New Group > create groups with the following titles:
    a) "Common Papers b/w X & Y"
    b) "Differences b/w X & Common Papers"
    c) "Differences b/w Y & Common Papers"
    d) "Conflict"
4) Combine both partners' libraries. Click on "All References" at the top of the left column. Go to References > Find duplicates > press CANCEL > all duplicates will be highlighted > right-click and move duplicate references into the "Common Papers b/w X & Y" group
5) Compare individuals' final library to the common library and file remaining references in "Differences b/w X & Common Papers" and "Differences b/w Y & Common Papers" accordingly.
    a)
        i) create a new library called "Common Papers b/w X & Y" and copy all references from the "Common Papers b/w X & Y" group into this library
        ii) Copy all of the references from individual X's library into the "Common Papers b/w X & Y" library
        iii) Search for duplicates, delete these, and file the remaining references into the "Differences b/w X & Common Papers" group in the "[Pathogen]_Combined" library
        iv) Delete duplicates in the "[Pathogen]_Combined" library
        v) Repeat steps i-iv for individual Y
6) Both partners should go through the two "Differences" groups and decide to include or exclude the references. Move included references into one group, excluded references into another group, and references you disagree on into the "Conflict" group.

7) Go through the "Conflict" library with the PI, and move references into the appropriate group.

PDF Search

1) File > New Library. Then File > Save As > title "[Pathogen]_PDF_Search_X"
2) Repeat title "[Pathogen]_PDF_Search_Y"
3) Copy and paste the first half of reference from the "[Pathogen]_Combined" library group ____ into the library "[Pathogen]_PDF_Search_X".
4) Copy and paste the second half of reference from the "[Pathogen]_Combined" library group ____ into the library "[Pathogen]_PDF_Search_Y".
5) Each partner works on their own library, and find the PDF's in their library. When a pdf is found, save the document in a separate folder, and also attach it to the reference in EndNote.
6) Search through Pubmed through the Emory library system. This works best on campus, logged into the University network, and logged into the library system.
7) Manually search the ____ library system using reference information from the EndNote library.
8) For articles that are only available in print, go to the library and make photocopies of the relevant articles. Scan these copies, save them as pdf's, and upload them to the appropriate Endnote reference.
9) For articles that are not available at Emory, go to http://www.library.emory.edu/uhtbin/nph-illiad > sign in using Emory username and password > under Create New Request click on "Copy of Article." Fill out the request. Be sure to use the full name of the journal, not the abbreviation

PDF Exclusions

1) In the library "[Pathogen]_PDF_Search _X" create the following group sets and groups:
   a) Set "Exclude"
      i) Not_full_year
      ii) Not_monthly_data
      iii) No_data
      iv) Outbreak (depending on pathogen)
   b) Set "Use"
      i) To Extract
      ii) Maybe
      iii) Have Extracted
      iv) Can't Extract
2) Go through each pdf. Place excluded references in the appropriate group based on why it was excluded, and place all included references in the "To Extract" group
3) Go to the separate folder of all pdf's. Create the following sub folders:
   a) [Pathogen]_Yes
   b) [Pathogen]_No
   c) [Pathogen]_Maybe
   d) [Pathogen]_Can't Extract
4) Transfer all pdf's into the appropriate subfolder.
   a) All references from the "Exclude" set group get placed in the "[Pathogen]_No" folder
   b) All references from the "To Extract" group get placed in the "[Pathogen]_Yes" folder

c) All references from the “Maybe” group get placed in the “[Pathogen]_Maybe” folder

5) Send the “[Pathogen]_Maybe” folder to the PI for final review and shift references and pdf’s to appropriate groups and subfolders

Regression Results (not including Australia data)

Bivariate analysis (without weighting since no acceptable way to weight in SAS)

Outcome	Predictor	Estimate	95% CI	p-value
Cases	Latitude	Infinite like.		
	Winter temp	Infinite like.		
	Peak/trough temp	0.002197	-0.00456 0.008950	0.5191
	Avg rain	Infinite like.		
Outbreaks	Latitude	-0.00456	-0.01268 0.003555	0.2663
	Winter temp	0.006666	-0.02154 0.03487	0.6391
	Peak/trough temp	0.002868	-0.00764 0.01338	0.5883
	Avg rain	0.008146	-0.00621 0.02250	0.2619

Bivariate analysis (with 3-level weighting)

Outcome	Predictor	Estimate	95% CI	p-value
Cases	Latitude	Infinite like.		
	Winter temp	Infinite like.		
	Peak/trough temp	Infinite like.		
	Avg rain	-0.00701	-0.01597 0.001953	0.1235
Outbreaks	Latitude	-0.00356	-0.01128 0.004159	0.3609
	Winter temp	Too many like.		
	Peak/trough temp	Too many like.		
	Avg rain	0.007905	-0.00835 0.02416	0.3356

R regression of one value per study, with and without all four confounders

Predictor	Estimate	95% CI	p-value	Stan error
Latitude	0.0005322	-0.00381, 0.004879	0.811	0.0022179
Winter temp	-0.005192	-0.01389, 0.003508	0.248	0.004439
Peak/trough temp	0.002084	-0.00418, 0.008348	0.517	0.003196
Avg rain	-0.0006765	-0.00785, 0.006497	0.854	0.0036599
(with all four confounders)				
Latitude	-0.0014534	-0.52201, 0.519102	0.699	0.2655895
Winter temp	-0.0097287	-0.02367, 0.004211	0.179	0.0071120
Peak/trough temp	0.0017390	-0.00518, 0.008661	0.625	0.0035315
Avg rain	-0.0027664	-0.01369, 0.008156	0.622	0.0055728