Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world-wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Taylor A. Moore Date

Characterizing Norovirus Seasonality in High Income Countries Using Wavelet Analysis

By

Taylor A. Moore

Master of Public Health

Global Epidemiology

Benjamin A. Lopman, PhD

Committee Chair

Kristen Bratton Nelson, PhD

Committee Member

Characterizing Norovirus Seasonality in High Income Countries Using Wavelet Analysis

By

Taylor A. Moore

B.S., The Ohio State University, 2017

Faculty Thesis Advisors: Benjamin A. Lopman, PhD; Kristin Bratton Nelson, PhD

An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Epidemiology

2020

Abstract

Characterizing Norovirus Seasonality in High Income Countries Using Wavelet Analysis

By: Taylor A. Moore

Norovirus is the leading cause of sporadic cases and outbreaks of acute gastroenteritis worldwide. The rapidly evolving genome of norovirus has resulted in the numerous worldwide pandemics with novel strains emerging every 3-4 years. Regional comparisons of seasonality could identify unique signatures in norovirus incidence patterns that correspond with molecular changes in circulating and emerging norovirus strains. There is a significant amount of evidence for the wintertime seasonality but there is limited data on inter-season variation as well as country level comparisons. We used data from the national surveillance systems from four high income countries, Germany, Japan, United Kingdom and United States, to estimate and compare the seasonality of norovirus incidence. Descriptive and wavelet analyses were used to identify country specific seasonal variations in emergent and non-emergent strain years, as well as country level comparisons of norovirus incidence. All four countries showed strong evidence for 12- month periodicity with peaks during the winter months, November to February, and low level or disappearance in summer months. There was variation in the effect of the emergence on a new strain on the norovirus incidence in different countries. The emergence of the 2012 Sydney strained was associated with increased levels of norovirus burden in all four countries. Other emergent strains such as 2006/7ab and 2010 New Orleans produced a significant increase of incidence in some countries but not all. Peak month and month of 50% case burden did not show strong correlation between countries. Norovirus is endemic globally but does not have a uniform effect. Identifying characteristic changes in norovirus incidence in years with or without novel variant strains may allow earlier warning for pandemic potential outbreaks and improve transmission prevention and control measures.

Characterizing Norovirus Seasonality in High Income Countries Using Wavelet Analysis

By

Taylor A. Moore

B.S., The Ohio State Univeristy, 2017

Faculty Thesis Advisors: Benjamin A. Lopman, PhD; Kristin Bratton Nelson, PhD

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Epidemiology

2020

Table of Contents

Background

Norovirus Overview

Norovirus is a highly infectious enteric pathogen, affecting all ages and present in various settings. It is the most common cause of diarrheal episodes globally and is consistently found as the primary cause of foodborne disease outbreaks, healthcare–acquired infection and a common cause of travel-associated diarrhea (Lopman, Steele, Kirkwood, & Parashar, 2016). Part of the *Caliciviridae* family, norovirus (NoV) is a small, non-enveloped, positive single stranded RNA virus that evolves rapidly, leading to broad genomic diversity. Norovirus can be classified into five genogroups and 40 genotypes, with varying capabilities for human infection. Most human norovirus infections are caused by genogroups I, II, and IV, with GII being the most prevalent and having the highest pandemic potential (White, 2014). The other genogroups are not typically associated with human infection, instead infecting animals such as pigs, bovine and canines (Robilotti, Deresinski, & Pinsky, 2015). High levels of diversity and the continual evolution of the genome resulting in antigenic changes in norovirus is largely due to the selective pressures of the human immune system resulting in the replacement of circulating dominant strains every 2-3 years (Robilotti et al., 2015; White, 2014).

Natural History

A norovirus infection causes inflammation of the stomach and or intestines, resulting in acute gastroenteritis. Infections are typically quick setting, begin 12 to 48 hours after exposure and lasting one to three days (Clinic, 2017). Common symptoms include diarrhea, vomiting, nausea and stomach pain. Extensive diarrhea, vomiting, and crying often leads to dehydration, especially in young children and older adults. Severe dehydration may require hospitalization in order to reintroduce fluids into the body intravenously (CDC, 2018). Norovirus is reintroduced into the environment by the shedding of the virus in fecal excretions. A long viral shedding period, ranging from 12 to 56 days and a low infectious dose, as little as 18 viral particles, allows easy and quick person to person transmission, often causing extensive

outbreaks in the absence of control measures (Lian et al., 2019). Natural susceptibility to norovirus varies among individuals and between genotypes (Hundessa et al., 2018). Based on challenge studies, a primary norovirus infection is estimated to confer immunity for 6 months to 2 years. Some studies show that norovirus antibodies may not give complete protection. This protection may not present infection but may aid in the prevention of the manifestation of disease (Simmons, Gambhir, Leon, & Lopman, 2013). Levels of cross immunity are not well known; therefore, it is common for a person to have several norovirus infections, of different genotypes in a lifetime (CDC, 2018).

Epidemiological Burden

Diarrheal diseases are ranked the second highest burden among all communicable diseases, resulting in an estimated 1.4 million yearly deaths and 89.5 million disability adjusted life years (DALYs) (Kreidieh, Charide, Dbaibo, & Melhem, 2017). Person to person transmission is most common in long term healthcare and hospital settings, such as nursing homes and outpatient centers (CDC, 2018). The infection spreads quickly and causes the most severe morbidity and mortality in children and older adults resulting in high burdens in hospitals and elderly care centers (Lian et al., 2019). In the United States, norovirus causes an average of 570–800 deaths, 56,000–71,000 hospitalizations, 400,000 emergency department visits, 1.7–1.9 million outpatient visits, and 19–21 million total illnesses per year (Ahmed, Lopman, & Levy, 2013). In Europe, norovirus is estimated to have caused 5.7 million infections, 800,000 medical visits, 53,000 hospitalizations and 102 deaths among children less than 5 years between 2003 and 2013. Globally, one fifth of acute gastroenteritis cases are attributable to norovirus (Mattison, Cardemil, & Hall, 2018). Estimates of the regional distribution of norovirus is typically limited to developed countries, such as United States, Europe and Japan, due to the lack of data from high mortality settings and low-income countries (Kreidieh et al., 2017).

Molecular Epidemiology

Norovirus has three open reading frames: ORF1 for viral RNA dependent RNA polymerase (RdR, ORF for viral protein 1 (VP1) and ORF for the minor capsid protein (VP2). On the surface of VP1 is subdomain P2, which is highly variable and houses the majority of the antigenic and histo-blood group antigen binding sites (Mathew, 2019). Of the three genogroups that cause human infections, GII.4 is the only one associated with global pandemics of gastroenteritis, accounting for 60-80% of all human infections of norovirus. It is thought that GII.4 viruses possess the ability to bind to a wider range of histo-blood group antigens resulting in a larger pool of susceptible than other genogroups. Most antigenic variations in GII.4 strains are localized to the five blockade epitopes (A-E) resulting in mutations that allow the virus to escape present herd immunities (White, 2014). GII.4 strains had an evolution rate that was 1.7 times that of other norovirus strains, supporting the idea that it undergoes antigenic drift at a faster rate (R. A. Bull, Eden, Rawlinson, & White, 2010). Between 2000 and 2010, GII.4 accounted for 62% of all norovirus outbreaks and caused 5 major global pandemics: US 1996, Farmington Hills 2002, Hunter 2004, Den Haag 2006b, New Orleans 2009 (Yu et al., 2015). The emergence of the novel GII.4 variant in 2012 as the current dominant strain, resulted in significant increases in norovirus incidence worldwide. The replication cycle and evolution of GII.4 strains are not fully understood, due to the lack of ex vivo cultures of the human virus, hindering the advancement of vaccine production (White, 2014).

Seasonality

Seasonality of infectious diseases can be defined as the appearance of recurrent epidemics at distinct times of time the year (Rohayem, 2009). Each disease has its own seasonal pattern which may vary among certain geographic locations, demographic groups or in the presence of other diseases. There are many factors that may play into the seasonal oscillation of disease incidence. Seasonal changes in effective contact rates, durability of pathogen in various environments, seasonal immune suppression or host susceptibility, as well as other climatic, social or biological factors may be driving forces of the seasonality of infectious diseases (Fisman, 2012). Norovirus typically follows an overall winter

seasonality, with peaks from December to February in the Northern Hemisphere and June to August in the Southern Hemisphere. A winter seasonality typically is associated with cooler temperatures and lower population immunity, increasing the opportunity for successful transmission (Ahmed et al., 2013). Despite the overall trend, there is evidence of regional differences in seasonality, overall and among different strains. From 2014 to 2017, Hong Kong experienced bimodal seasonality and alternating predominance of GII.4 and non-GII.4 genotypes resulting in GII.4 dominating the summer and autumn months and non-GII.4 dominating in the winter months (Chan et al., 2018). From 2004 to 2006, norovirus in Australia reached seasonal peaks in the autumn months, March to May (Tu et al., 2007).

Regional differences and the increasing influence of climate change calls into question the effect of climatic factors on the transmission and seasonality of norovirus. There is evidence that rainfall could be an important predictor of norovirus seasonality due to heightened seasonal strength during the wettest months. The association between norovirus and temperature mediated transmission remain inconclusive. With currently available data, analysis of meteorological and demographic differences are typically limited to higher income countries such as in Europe and Asia, due to the lack of long term data from tropical regions (Ahmed et al., 2013).

Introduction

Norovirus is the leading cause of sporadic cases and outbreaks of acute gastroenteritis worldwide. It is a highly infectious pathogen that spreads through fecal-oral transmission, the consumption of contaminated food or water or from contact with contaminated surfaces (Ahmed et al., 2014) . Person to person transmission is most common in long term healthcare and hospital settings, such as nursing homes and outpatient centers (CDC, 2018). The infection spreads quickly and causes the most severe morbidity and mortality in children and older adults resulting in high burdens in hospitals and elderly care centers (Lian et al., 2019). The rapidly evolving genome of norovirus has resulted in the numerous worldwide pandemics with novel strains emerging every 3-4 year (R. A. Bull et al., 2010). Identifying characteristic

changes in norovirus incidence in years with or without novel variant strains may allow earlier warning for pandemic potential outbreaks and improve preparation for hospital surges.

Norovirus typically follows an overall winter seasonality, with peaks from December to February in the Northern Hemisphere and June to August in the Southern Hemisphere. A winter seasonality typically is associated with cooler temperatures and lower population immunity, increasing the opportunity for successful transmission (Ahmed et al., 2013). However, seasonal variation in norovirus infection remains poorly understood. There is yet to be an explanation for the occurrence of outbreaks during winter months and the near disappearance of outbreaks during summer months (Rohayem, 2009).

Norovirus is a single stranded RNA virus comprised of a genome with five genogroups and 40 genotypes, with varying capabilities of human infection. Most human norovirus infections are caused by genogroups I, II, and IV, with GII being the most prevalent and having the highest pandemic potential (White, 2014). Genogroup II genotype IV (GII.4) norovirus is associated with multiple global pandemics of gastroenteritis: US95 (1996), Farmington Hills (2002), Hunter (2004), 2006a/b virus (2006/2007), New Orleans (2010) and Sydney (2012). As of 2012, the GII.4 Sydney is the most predominate strain circulating worldwide (Thongprachum et. al, 2016). GII.4 strains accounts for 60-80% of all human infections. Studies show that GII.4 strains possess the ability to bind to a wider range of histo-blood group antigens than other genogroups, resulting in a larger pool of susceptible individuals (White, 2014). GII.4 strains have an evolution rate that is 1.7 times that of other norovirus strains, supporting the idea that it undergoes antigenic drift at a faster rate, resulting in the subsequent appearance of novel variant strains (Yu et al., 2015).

Regional comparisons of seasonality could identify unique signatures in norovirus incidence patterns that correspond with molecular changes in circulating and emerging norovirus strains. There is a significant amount of evidence for the wintertime seasonality but there is limited data on inter-season variation as well as country level comparisons. Understanding the variation in norovirus seasonality can provide valuable information that can inform current strategies on norovirus surveillance, hospital

preparedness and vaccine development and administration. Variations in timing and peaks of season may lead to an influx of cases at certain points of the year. If this varies by country, further research could be done to identify possible causal links to target norovirus interventions. If the time series data shows a similar periodicity, a model could be created to predict future seasons and anticipate the most effective times to administer vaccines and increase awareness campaigns. This study will use national surveillance data from four high income countries, Germany, Japan, United Kingdom and United States, to estimate and compare the seasonality of norovirus incidence. Descriptive and wavelet analyses will be used to identify intra-country seasonal variations in emergent and non-emergent strain years, as well as inter-country seasonal variations in norovirus incidence.

Methods

Surveillance Data:

We used national norovirus surveillance data from Germany, Japan, United Kingdom and United States.

Germany: Norovirus is a reportable disease in Germany. We used the SurvStat database, maintained by the Robert Koch Institute, to abstract weekly data on confirmed cases of norovirus (stool specimen positive for norovirus) from 2001-2019.

Japan: We used data obtained from the Infectious Agents Surveillance Report (IASR) of National Institute of Infectious Diseases (NIID) on weekly laboratory reports of norovirus (GII.4 and non-typable GII) from 1999-2014. Typed and non-typed reported cases were aggregated to compute total laboratory reported norovirus cases in Japan.

United Kingdom: We used data from Public Health England (PHE) on weekly laboratory reports of norovirus cases from 1996 to 2016.

United States: We used norovirus surveillance data from the National Outbreak Reporting System (NORS) operated by the Center for Disease Control and Prevention (CDC). This data was reported as the number of norovirus outbreaks per month from 2009-2018. NORS defines an outbreak as an occurrence of two or more similar illnesses resulting from a common exposure that is either suspected or laboratory-confirmed to be caused by norovirus.

Time Series and Wavelet Analysis

For each country, norovirus case and outbreak data were aggregated into monthly counts. To quantify seasonal patterns in norovirus, the monthly data was plotted in time series for each country. The periodicities of the time series data were assessed using wavelet analysis of the time series data via the WaveletComp package in R i386 3.6.0 . Wavelet analysis allows the identification of significant patterns or changes in time signatures using a continuous Morlet wavelet transform. Average wavelet power plots using a statistical significance level of 0.05 were used to identify significant temporal periodicity in each country. (Figures 15-18)

Statistical Analysis

Cumulative case or outbreak percentages were calculated by season for each country. Peak month for each season was defined by the month with the highest number of norovirus cases. The month of 50% season burden was defined as the month where at least 50% of the cases for that season year were reported. Peak month and month of 50% burden were extracted and plotted to visualize variation between countries. R^2 correlation values were calculated using Excel.

Results

Characterizing Seasonality

Japan

Based on 15 seasons from 2000 to 2014, the typical norovirus season in Japan peaked in December (67%, n = 10). Two seasons (2002-2003, 2004-2005) peaked in November and two seasons (2004-2005, 2009-2010) peaked in January (Figure 3). The average peak count was 690 cases (Table 2). The majority of cases occurred between November and February with 50% of cases being reached by December (43%, n = 6) or January (57%, n = 8) (Figure 4). Four seasons showed significant variation from the average season.

The 2006 – 2007 season in Japan had the highest burden of cases. The season peaked in December with a peak count of 1,559, which was 2.25 times higher than average (Figure 1a). The season also showed an earlier start in October with 351 cases, approximately 5 times the average October case count of 71 cases. Typically, there is a constant decline in cases after the peak week but a secondary peak in April resulted in 134 cases (Figure 1a). The 2012-2013 season had the second largest norovirus burden. It peaked in December with a total case count 1,059, 1.5 times higher than the average (Figure 1a). The season also had an early October start with 117 cases, 1.6 times the average (Figure 1a). There was a secondary peak in May resulting in 130 cases. The 2004-2005 and 2007-2008 seasons also had secondary cases in May (173 cases) and April (155 cases), respectively. The average case counts in April and May were 104 and 94.

Germany

Based on 17 seasons from 2001 – 2018, the typical norovirus season in Germany peaked in January (59%, n = 10). Four seasons (2001-2001, 2006-2007, 2009-2010, 2011-2012) peaked in February and three seasons (2003-2004, 2005-2006, 2010-2011) peaked in March (Figure 3). The average peak count was 14,946 (Table 2). Most cases occurred between December to March with 50% of cases

typically reached in January (47%, n = 8) or February (35%, n = 6). The 2016-2017 season reached 50% of cases in December and the 2001-2002 season reached the threshold in March. (Figure 4)

Two seasons showed significant variation in peak count and burden. The 2007-2008 season had the largest burden of norovirus cases, resulting in peak count of 34,767 cases, 2.32 times higher than the average peak count. The rest of the season followed normal timing. The 2009-2010 season had the second largest burden, resulting in a peak count of 34,612 which was 2.32 times higher than average. January to March had an unusually high case burden, resulting in 65% of the reported norovirus cases, compared to the 47% average for the same time period in other seasons. January to March also had higher case counts than the peaks of 15 of the 17 seasons.

United Kingdom

Based on 19 seasons from 1996 - 2015, the typical norovirus season in the United Kingdom peaked in January (53%, n = 10). Four seasons (1996-1997, 1999-2000, 2005-2006, 2011-2012) peaked in February, three seasons (2000-2001, 2003-2004, 2010-2011) peaked in March, one season (2012-2013) peaked in December and one season (2002-2003) peaked in October (Figure 3). The average peak count was 956 cases (Table 2). Three seasons (2007-2008, 2011-2012, 2012-2013, 2013-2014) had a secondary peak in April and one season (2013-2014) peaked again in March (Figure 1c). The majority of cases occurred between December and March with 50% of cases being reached by January (42%, n = 8) or February (37%, n = 7). The 1997-1998 and 2002-2003 seasons reached 50% case burden in December and the 2003-2004 season reached that level in March. (Figure 4)

The 2009-2010 season was the highest burden season. The number of reported cases in January, February and March were higher than the peak counts of all other 18 seasons. During this season, there was a substantial increase in cases from the relatively average December case count to the January peak count of 3,107 cases, which was 3.25 times higher than the average peak count. The 2009-2010 season also had a secondary peak in March that was 3.78 times the average case count for May. The 2012-2013

season exhibited an uncharacteristic pattern. It had an early peak month in December with 1,599 cases and a decrease in cases in January, February and March, leading to a secondary peak in April of 1,380 cases. In the opposite trend, the 2014-2015 season's January to April months saw little decrease in the number of cases, with all four months reporting case counts near the January peak of 1,194 cases.

United States

Based on 9 seasons, the typical norovirus season in the United States peaked in January (56%, n = 5). Two seasons (2010-2011, 2014-2015) peaked in February and two seasons (2013-2014, 2015-2016) peaked in March (Figure 3). The average peak outbreak count was 139 (Table 2). The 2012-2013 season experienced a secondary peak in March (Figure 1d). The majority of outbreaks occur between December and March with 50% of outbreaks usually reached by January (44%, n= 4). The 2009-2010, 2013-2014, and 2014-2015 seasons reached 50% of outbreaks in February and the 2015-2016 season reached that level in March (Figure 4).

The 2011-2012 and 2012-2013 seasons experienced the greatest burden of outbreaks resulting in a peak count of 251 and 232 outbreaks, respectively. After the 2012-2013 outbreaks, the norovirus outbreak burden decreases. Post-2012, the 2014-2015 season had the highest peak count of 150, which was 1.67 times smaller than the peak count in 2011-2012.

Inter-Country Comparisons

Overall, the distribution of peak months varied between countries. The peak months in Germany and Japan had no correlation ($R^2 = 0$). The United Kingdom and the United States had the strongest positive correlation ($R^2 = 0.52$) and Japan and the United Kingdom had the strongest negative correlation ($R^2 = -0.69$). The month that 50% of cases were reached showed weak to moderate positive correlation between the countries. Japan and the United States had the highest correlation ($R^2 = 0.61$) and (Table 3). Japan typically had an earlier peak month and month of 50% cases reached through the entire time period (Figures 3, 4).

Wavelet Analysis

The univariate wavelet analysis showed a strong 12-month periodicity in norovirus seasonality in all four countries with average wavelet peak power greater than 0.6 (Figures 5-8). Japan showed evidence of a significant 6-month periodicity from 2006-2009 and 2013-2014 (Figure 5b).

Discussion

We analyzed the seasonality of reported norovirus incidence in Germany, Japan, United Kingdom and United States. The overall descriptive results showed consensus with prior studies suggesting that norovirus has a strong winter seasonality. All four countries reported highest norovirus incidence in winter months, November to February, and low levels or disappearance of cases/outbreaks in the summer months. The wavelet analysis confirmed the annual cyclic nature of norovirus dynamics with a 12-month periodicity. Despite the similarities, there were notable differences in season timing and seasonal characteristics during emergent strain years between the different countries.

Years with pandemic emergent strains did not have the same effect in all countries. The emergence of the 2006a/b GII.4 appears to have a strong effect on the increased incidence of norovirus cases during the 2007-2008 season in Japan and the 2007-2008 season in Germany. The emergence of the 2010 New Orleans strain had a strong effect on the 2009-2010 season in the United Kingdom and the 2009-2010 season in Germany. The 2012 Sydney strain had a significant effect in all four countries. In Japan the second highest burden season was in 2012-2013. In Germany the third highest burden season was in 2011-2012. In the United Kingdom, the second and fourth highest burden seasons were in 2011-2012 and 2012-2013, respectively and the United States and the first and second highest burden seasons in 2011-2012 and 2012-2013, respectively. Despite being labeled global pandemic strains, there were country to country variation in the increased burden associated with their emergence.

Between countries there was a significant variation in seasonal peak months and months of 50% case burden, even among emergent strain years. The 2006-2007 season in Japan and the 2012-2013

season in the United Kingdom had earlier peaks in November and December, respectively, which differed from the expected December and January peaks, respectively. The 2009-2010 and 2011-2012 season in Germany and the 2011-2012 season in the United Kingdom had late February peak months, which differed from the expected January peak month for both countries. The 2009-2010 and 2011-2012 season in Germany had 2 of 3 seasons peak in February. The 2012-2013 season in the United Kingdom was the only season to peak in December. Even with changes in peak month, they were not outliers when considering the variation seen in other seasons within the country. Based on these results, sudden changes in peak month are not indicative of a warning for a new emergent strain or increase in norovirus incidence.

While genotype data was not included in this study, there are numerous studies that document the molecular epidemiology of novel GII.4 strains. A study by Bull et. al compared the genomic and antigenic diversity of norovirus samples in Wales, Australia the pandemic strains US95/96 and Farmington Hills in other countries. They found that strains isolated in Australia were similar to the genetic makeup and the outbreak timing seen in other countries in the Northern Hemisphere (Rowena A. Bull, Tu, McIver, Rawlinson, & White, 2006). The results of this study show that norovirus seasonality and increased incidence due to novel strain circulation can be seen across multiple countries, but the effect varies. The proportion of GII.4 strains and other circulating strains most likely have effect on the transmission and observed incidence seen in a country. A recent study shows that the proportion of GII.4 in Japan during the 2006-2007 and 2012-2013 seasons was 80% of GII strains but less than 50% in the 2008–2009, 2009–2010, 2010–2011, and 2013–2014 seasons (Kumazaki & Usuku, 2015). This is consistent with the trends seen in this study. The emergence of the 2006a/b and the Sydney 2012 strains had a more notable increase in norovirus incidence than in other emergent strain years, likely due to the GII.4 to non-GII.4 proportions. When understanding norovirus seasonality and the implications of novel strains, the genomic diversity of each country should be considered to assess the severity of emergence in the population. Further comparative research could be done to estimate the genomic variation in strains

between countries to assess the effects of certain recombinant genes on transmission and the overall epidemiology of norovirus.

This study is limited by the robustness of each surveillance system. Varying time periods and different methods of data collection, either over time or between countries, may result in skewed norovirus incidence data. The month of case incidence and the reported month of case may differ due to reporting delays in surveillance systems. Norovirus case and outbreak counts were aggregated my month in to minimize the reporting bias. Despite these limitations, this study confirmed overall trends supported previous evidence of wintertime seasonality and highlighted country-specific variation in norovirus incidence.

Norovirus is endemic all over the globe. A quickly evolving genome and numerous modes of transmission allows it to evade current public health efforts of control and vaccine production. Currently, containment of outbreaks is the largest defense against norovirus incidence. Understanding the seasonality of norovirus could identify significant characteristics that give further insight on transmission dynamics. This paper concludes that while general trends of norovirus remain true from a multilevel perspective, a closer look at country level incidence could reveal important variations and determine why pandemic strains do not affect norovirus incidence uniformly. Further research should be done to identify country specific traits such as, genomic diversity, population immunity, surveillance, or control measures. More country level comparisons could provide a valuable learning opportunity in understanding norovirus transmission dynamics and improve control measures.

References

Ahmed, S. M., Hall, A. J., Robinson, A. E., Verhoef, L., Premkumar, P., Parashar, U. D., . . . Lopman, B. A. (2014). Global prevalence of norovirus in cases of gastroenteritis: a systematic review and meta-analysis. *The Lancet Infectious Diseases, 14*(8), 725-730. doi:10.1016/S1473-3099(14)70767-4

Ahmed, S. M., Lopman, B. A., & Levy, K. (2013). A Systematic Review and Meta-Analysis of the Global Seasonality of Norovirus. *PLoS ONE, 8*(10), 1-7. doi:doi:10.1371/journal.pone.0075922

Bull, R. A., Eden, J. S., Rawlinson, W. D., & White, P. A. (2010). Rapid evolution of pandemic noroviruses of the GII.4 lineage. *PLoS Pathog, 6*(3), e1000831. doi:10.1371/journal.ppat.1000831

Bull, R. A., Tu, E. T. V., McIver, C. J., Rawlinson, W. D., & White, P. A. (2006). Emergence of a new norovirus genotype II.4 variant associated with global outbreaks of gastroenteritis. *Journal of clinical microbiology, 44*(2), 327-333. doi:10.1128/JCM.44.2.327-333.2006

Chan, M. C.-W., Kwok, K., Zhang, L.-Y., Mohammad, K. N., Lee, N., Lui, G. C. Y., . . . Chan, P. K. S. (2018). Bimodal Seasonality and Alternating Predominance of Norovirus GII.4 and Non-GII.4, Hong Kong, China, 2014-2017(1). *Emerging infectious diseases, 24*(4), 767-769. doi:10.3201/eid2404.171791

Clinic, M. (2017, Nov, 17, 2017). Norovirus Infection. Retrieved from https://www.mayoclinic.org/diseases-conditions/norovirus/symptoms-causes/syc-20355296

Fisman, D. (2012). Seasonality of viral infections: mechanisms and unknowns. *Clinical Microbiology and Infection, 18*(10), 946-954. doi:https://doi.org/10.1111/j.1469-0691.2012.03968.x

Hundessa, S., Williams, G., Li, S., Liu, D. L., Cao, W., Ren, H., . . . Guo, Y. (2018). Projecting potential spatial and temporal changes in the distribution of Plasmodium vivax and Plasmodium falciparum malaria in China with climate change. *The Science of the total environment, 627*, 1285-1293. doi:10.1016/j.scitotenv.2018.01.300

Kreidieh, K., Charide, R., Dbaibo, G., & Melhem, N. M. (2017). The epidemiology of Norovirus in the Middle East and North Africa (MENA) region: a systematic review. *Virology journal, 14*(1), 220-220. doi:10.1186/s12985-017-0877-3

Kumazaki, M., & Usuku, S. (2015). Genetic Analysis of Norovirus GII.4 Variant Strains Detected in Outbreaks of Gastroenteritis in Yokohama, Japan, from the 2006-2007 to the 2013-2014 Seasons. *PLoS ONE, 10*(11), e0142568-e0142568. doi:10.1371/journal.pone.0142568

Lian, Y., Wu, S., Luo, L., Lv, B., Liao, Q., Li, Z., . . . Ran, L. (2019). Epidemiology of Norovirus Outbreaks Reported to the Public Health Emergency Event Surveillance System, China, 2014–2017. *Viruses, 11*(4), 342. doi:10.3390/v11040342

Lopman, B. A., Steele, D., Kirkwood, C. D., & Parashar, U. D. (2016). The Vast and Varied Global Burden of Norovirus: Prospects for Prevention and Control. *PLoS medicine, 13*(4), e1001999-e1001999. doi:10.1371/journal.pmed.1001999

Mattison, C. P., Cardemil, C. V., & Hall, A. J. (2018). Progress on norovirus vaccine research: public health considerations and future directions. *Expert review of vaccines, 17*(9), 773-784. doi:10.1080/14760584.2018.1510327

Robilotti, E., Deresinski, S., & Pinsky, B. A. (2015). Norovirus. *Clinical microbiology reviews, 28*(1), 134-164. doi:10.1128/CMR.00075-14

Rohayem, J. (2009). Norovirus seasonality and the potential impact of climate change. *Clinical Microbiology and Infection, 15*(6), 524-527. doi:https://doi.org/10.1111/j.1469-0691.2009.02846.x

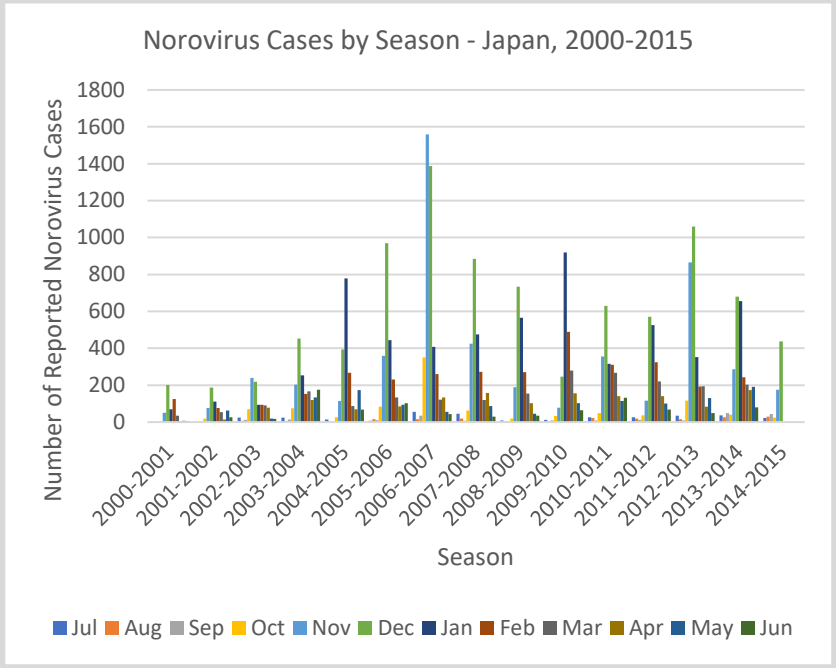
Simmons, K., Gambhir, M., Leon, J., & Lopman, B. (2013). Duration of immunity to norovirus gastroenteritis. *Emerging infectious diseases, 19*(8), 1260-1267. doi:10.3201/eid1908.130472

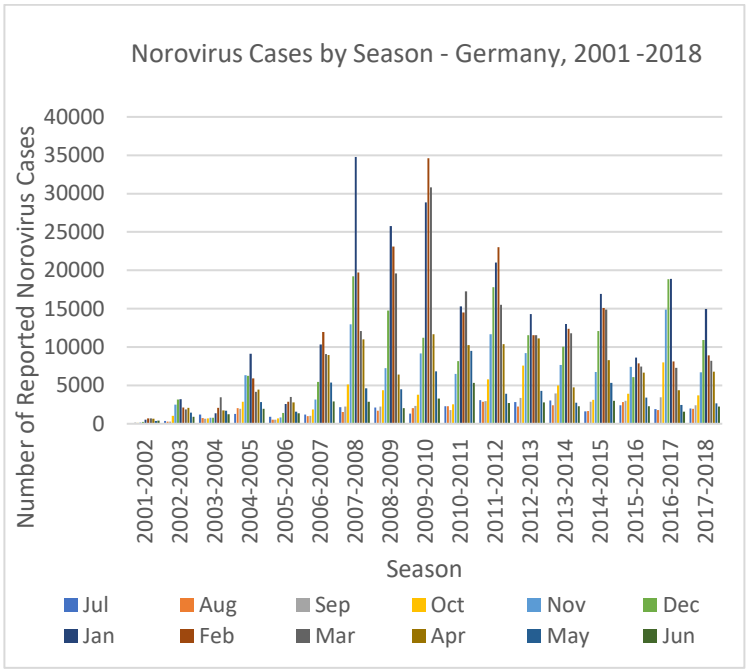
Tu, E. T. V., Nguyen, T., Lee, P., Bull, R. A., Musto, J., Hansman, G., . . . McIver, C. J. (2007). Norovirus GII.4 strains and outbreaks, Australia. *Emerging infectious diseases, 13*(7), 1128-1130. doi:10.3201/eid1307.060999

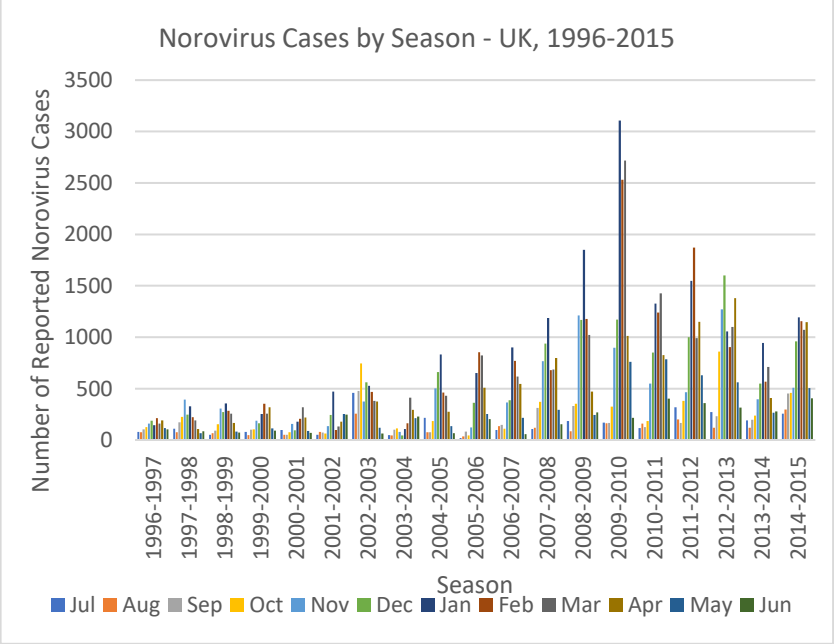
White, P. A. (2014). Evolution of norovirus. *Clinical Microbiology and Infection, 20*(8), 741-745. doi:10.1111/1469-0691.12746

Yu, Y., Cai, H., Hu, L., Lei, R., Pan, Y., Yan, S., & Wang, Y. (2015). Molecular epidemiology of oyster-related human noroviruses and their global genetic diversity and temporal-geographical distribution from 1983 to 2014. *Applied and environmental microbiology, 81*(21), 7615-7624. doi:10.1128/AEM.01729-15

Figures and Tables







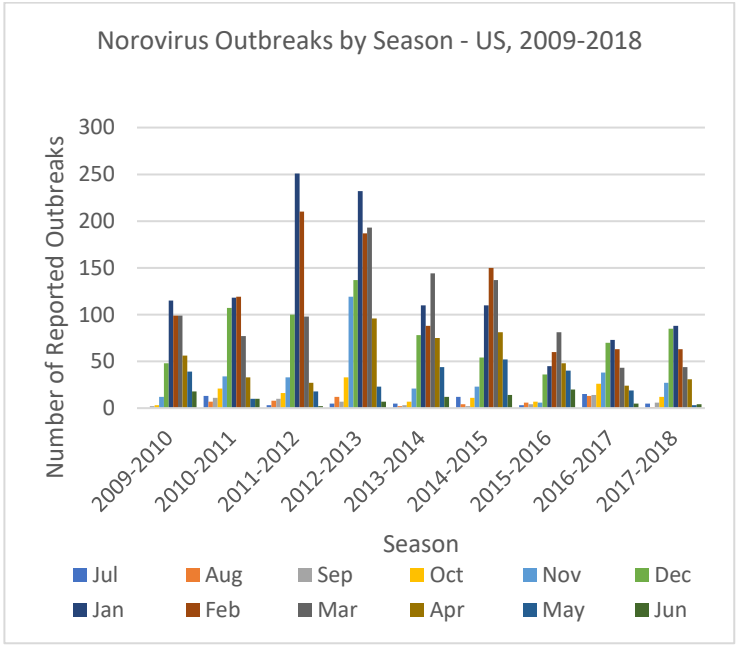
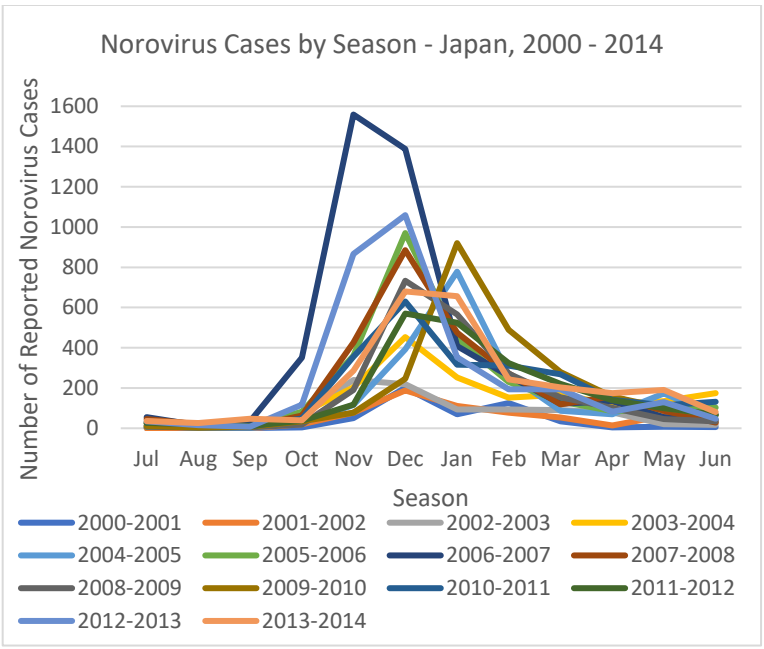
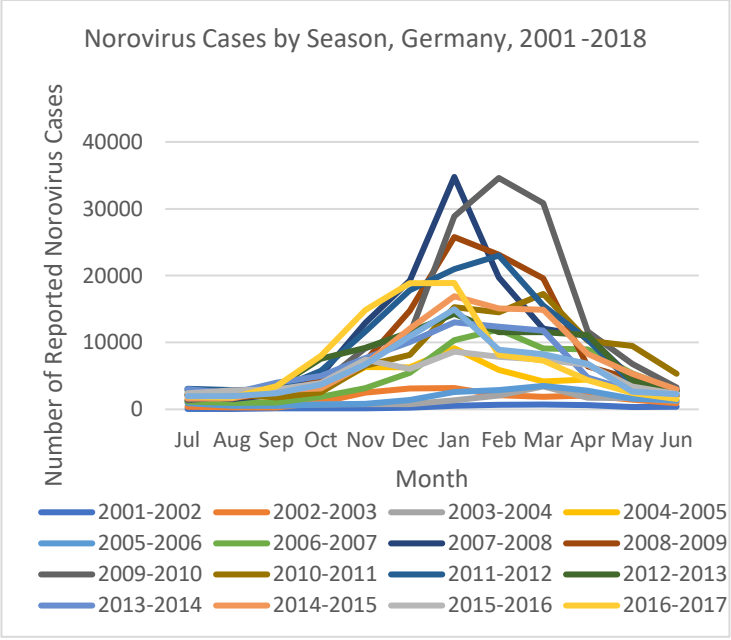
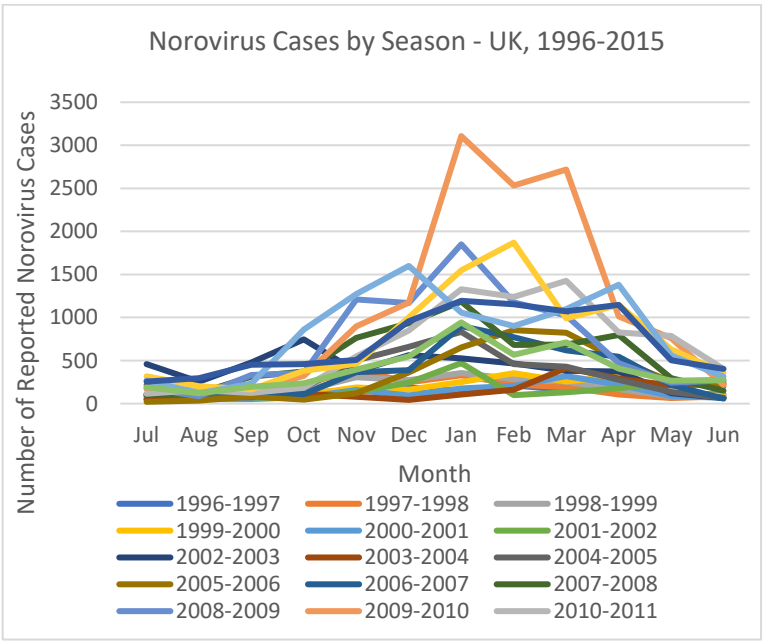


Figure 1. The monthly distribution of norovirus cases/outbreaks by season in A) Japan from 2000 to 2014, B) Germany from 2001-2018, C) United Kingdom from 1996-2015, and C) United States from 2009-2018. Season defined as July to June.







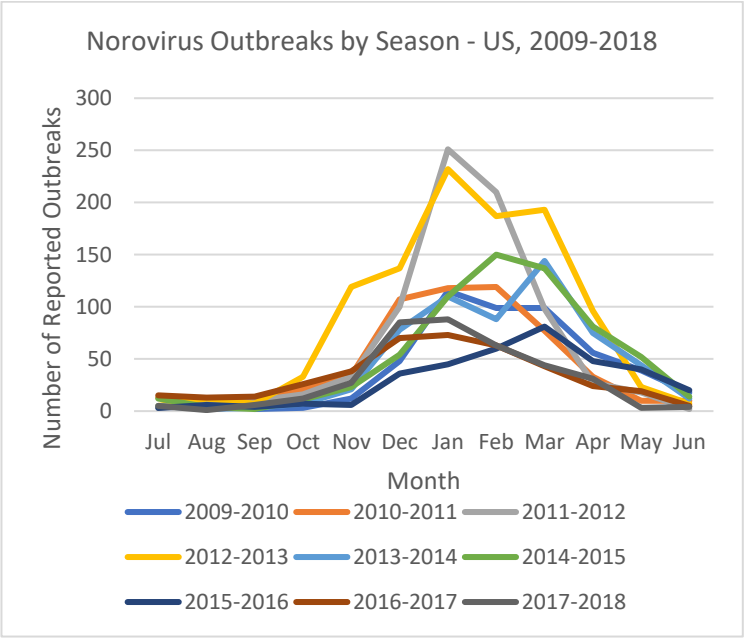


Figure 2. The monthly distribution of norovirus cases/outbreaks in A) Japan from 2000 to 2014, B) Germany from 2001-2018, C) United Kingdom from 1996-2015, and C) United States from 2009-2018. Season defined as July to June.

Table 1: Peak Month and Percentage of Total Count of Each Season

Season	Japan	Germany	United Kingdom	United States*
1996-1997	-	-	Feb 13%	-
1997-1998	-	-	Nov 18%	-
1998-1999	-	-	Jan 16%	-
1999-2000	-	-	Feb 17%	-
2000-2001	Dec 40%	-	Mar 20%	-
2001-2002	Dec 30%	Feb 17%	Jan 23%	-
2002-2003	Nov 25%	Jan 16%	Oct 16%	-
2003-2004	Dec 26%	Mar 21%	Mar 22%	-
2004-2005	Jan 39%	Jan 19%	Jan 21%	-
2005-2006	Dec 38%	Mar 18%	Feb 22%	-
2006-2007	Nov 35%	Feb 19%	Jan 21%	-
2007-2008	Dec 34%	Jan 27%	Jan 19%	-
2008-2009	Dec 36%	Jan 23%	Jan 22%	-
2009-2010	Jan 38%	Feb 24%	Jan 23%	Jan 23%
2010-2011	Dec 27%	Mar 18%	Mar 18%	Feb 22%
2011-2012	Dec 26%	Feb 19%	Feb 21%	Jan 32%
2012-2013	Dec 34%	Jan 15%	Dec 17%	Jan 22%
2013-2014	Dec 26%	Jan 16%	Jan 19%	Mar 24%
2014-2015	-	Jan 18%	Jan 14%	Feb 23%
2015-2016	-	Jan 14%	-	Mar 23%
2016-2017	-	Jan 21%	-	Jan 18%
2017-2018	-	Jan 21%	-	Jan 24%

*United States reports norovirus outbreaks, defined as an occurrence of two or more similar illnesses resulting from a common exposure that is either suspected or laboratory-confirmed to be caused by norovirus.

Table 2: Typical Season Peak Month and Average Count

	Japan	Germany	United Kingdom	United States*
Typical Peak Month	Dec 67% (10/15)	Jan 59% (10/17)	Jan 47% (9/19)	Jan 56% (5/9)
Average Peak Count	690	14,946	956	139

*United States reports norovirus outbreaks, defined as an occurrence of two or more similar illnesses resulting from a common exposure that is either suspected or laboratory-confirmed to be caused by norovirus.

Table 3: Season Correlation Coefficients

	Peak Month	Month 50% of Cases Reached
Country Comparison	**R^2**	**R^2**
Japan vs. Germany	0	0.17
Japan vs. UK	0.49	0.20
Japan vs. US*	-0.69	0.61
Germany vs. UK	0.36	0.47
Germany vs. US*	-0.21	0.44
UK vs. US*	0.52	0.25

*United States reports norovirus outbreaks, defined as an occurrence of two or more similar illnesses resulting from a common exposure that is either suspected or laboratory-confirmed to be caused by norovirus.

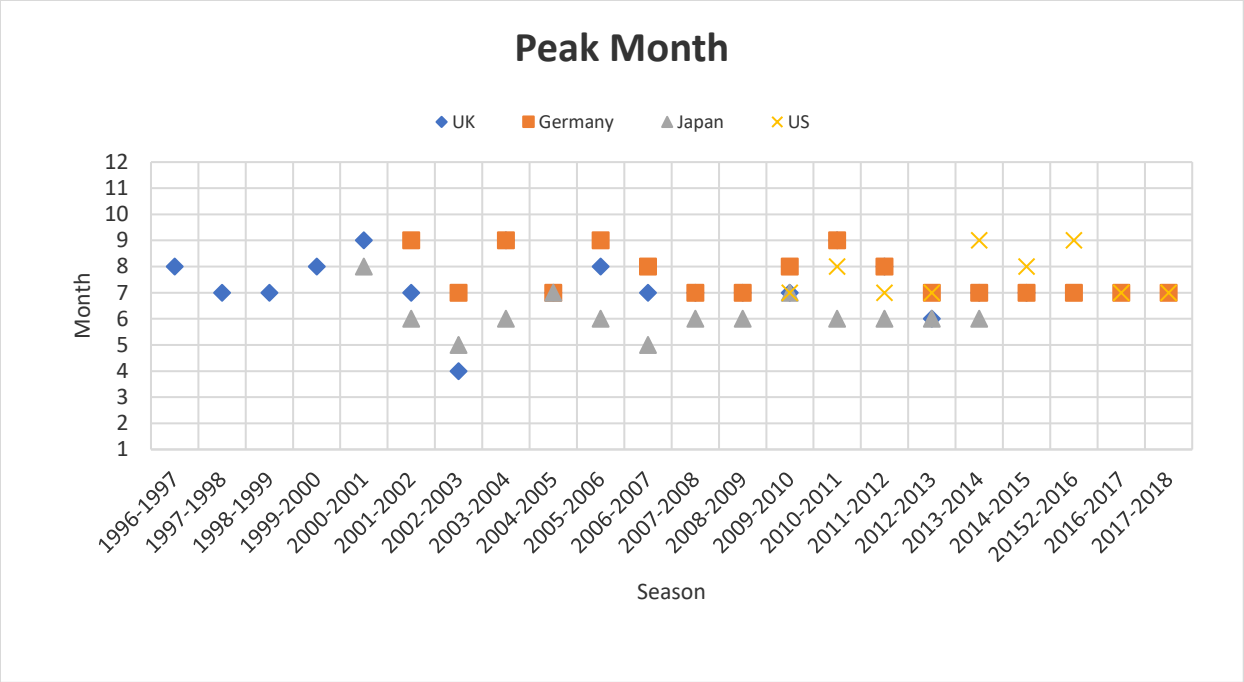


Figure 3.. The distribution of peak month in the United Kingdom, Germany, Japan and the United States. United States reports norovirus outbreaks, defined as an occurrence of two or more similar illnesses resulting from a common exposure that is either suspected or laboratory-confirmed to be caused by norovirus.

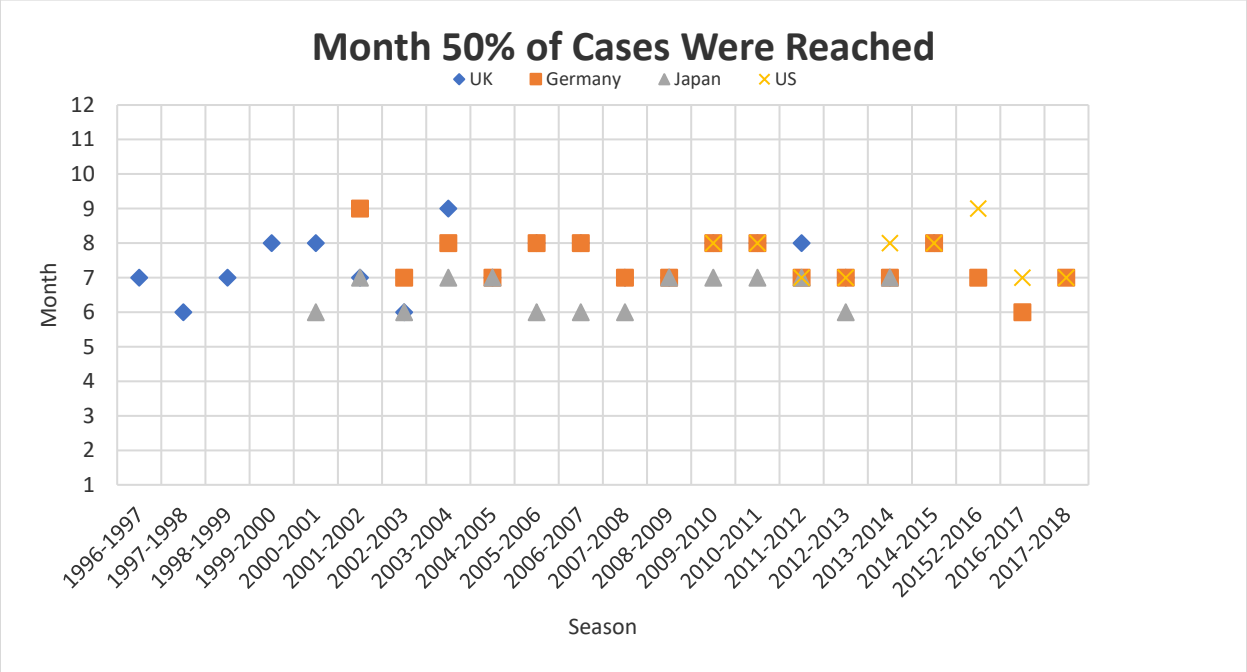


Figure 4. The distribution of month 50% of cases or outbreaks for the season were reached in the United Kingdom, Germany, Japan and the United States. United States reports norovirus outbreaks, defined as an occurrence of two or more similar illnesses resulting from a common exposure that is either suspected or laboratory-confirmed to be caused by norovirus.

Wavelet Analysis

Japan

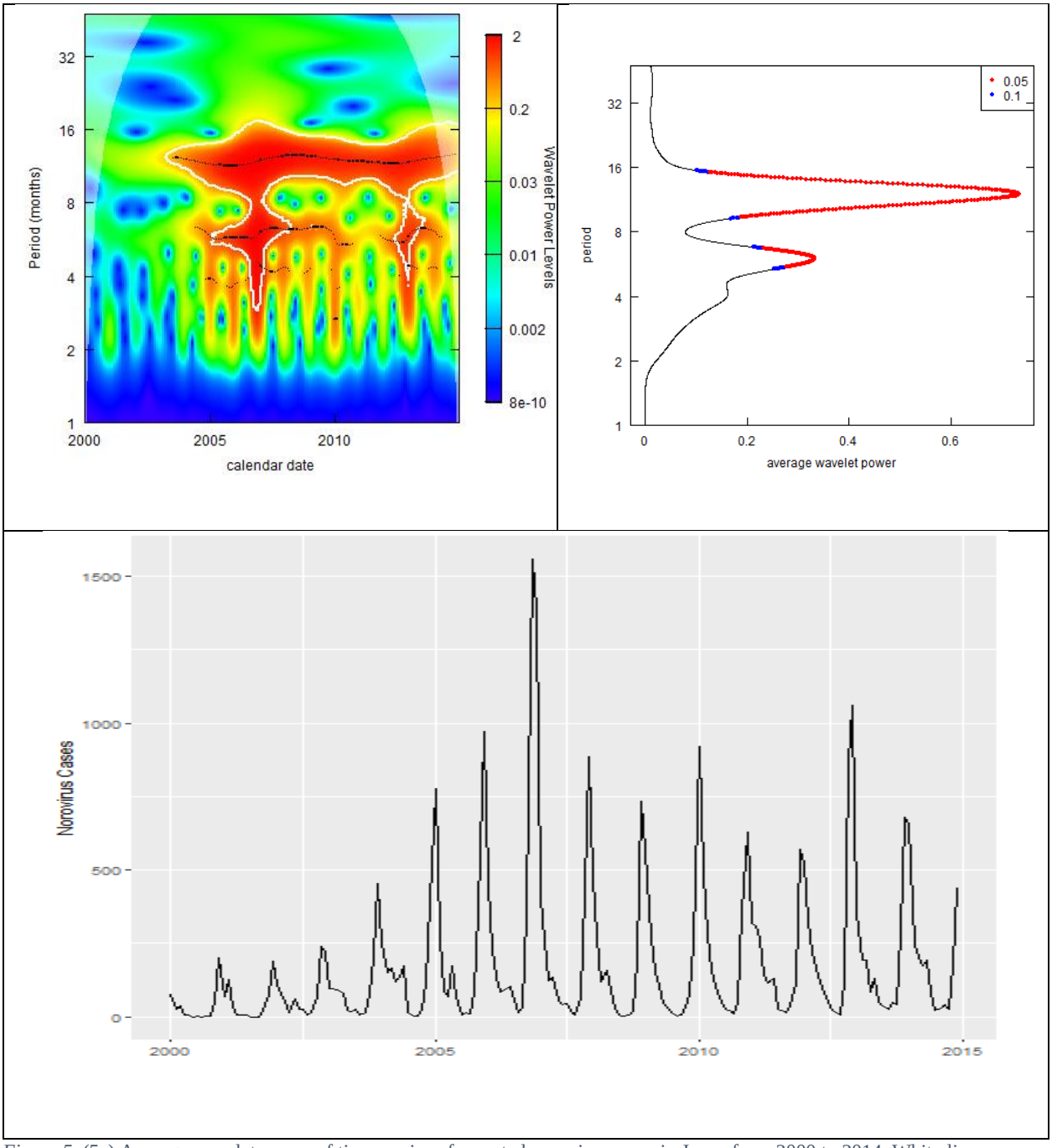


Figure 5. (5a) Average wavelet power of times series of reported norovirus cases in Japan from 2000 to 2014. White line represents statistical significance (p = 0.05). Black line represents the ridge of wavelet power highlighting the highest level of power in the spectrum. (5b) Average wavelet plot of time series by period. Significant levels of power are highlighted as red (p = 0.05) and blue (0.01). (5c). Time series for reported norovirus cases in Japan from 2000 to 2014.

Germany

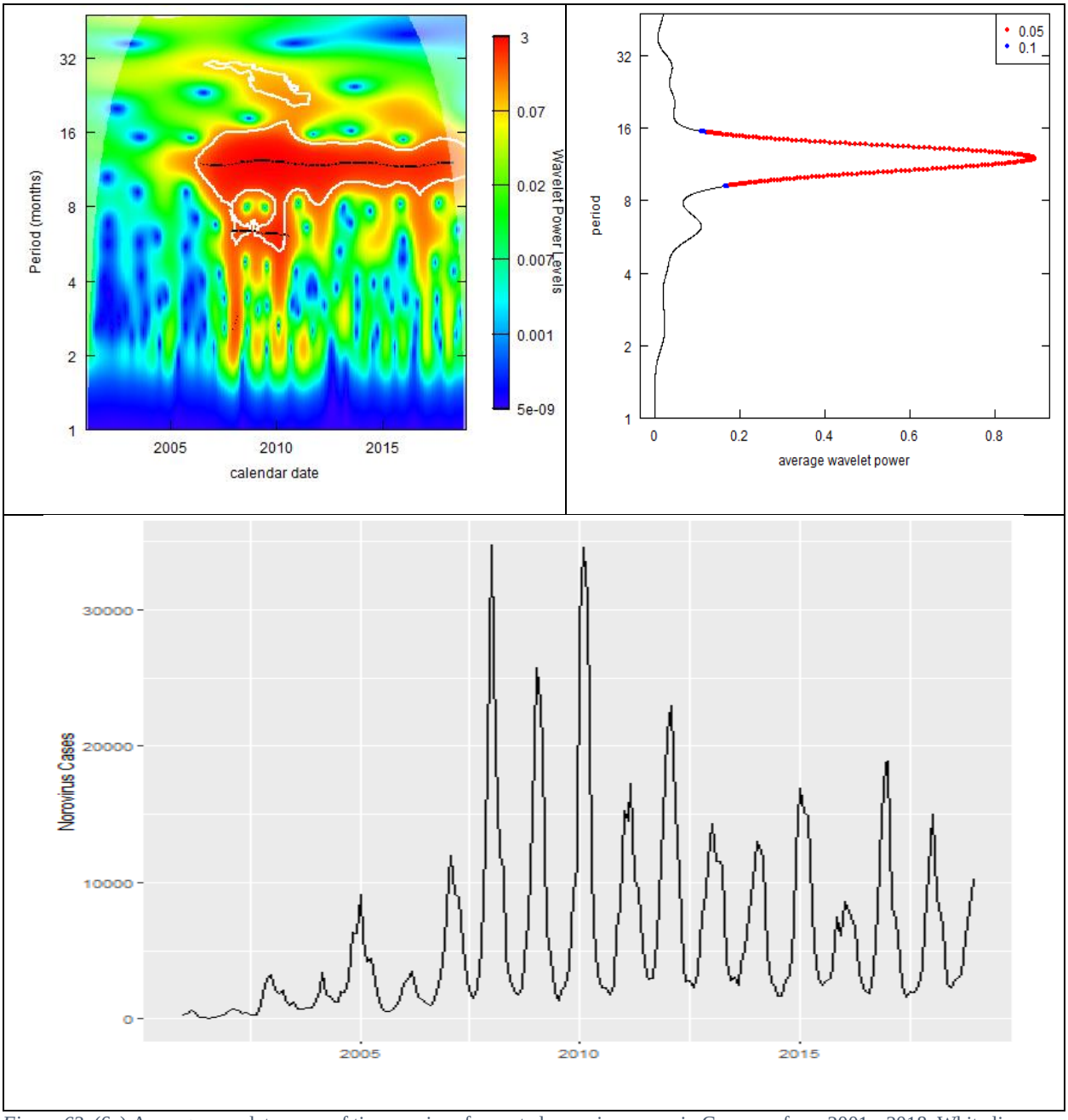


Figure 63. (6a) Average wavelet power of times series of reported norovirus cases in Germany from 2001 - 2018. White line represents statistical significance (p = 0.05). Black line represents the ridge of wavelet power highlighting the highest level of power in the spectrum. (6b) Average wavelet plot of time series by period. Significant levels of power are highlighted as red (p = 0.05) and blue (0.01). (6c). Time series for reported norovirus cases in Germany from 2001-2018.

United Kingdom

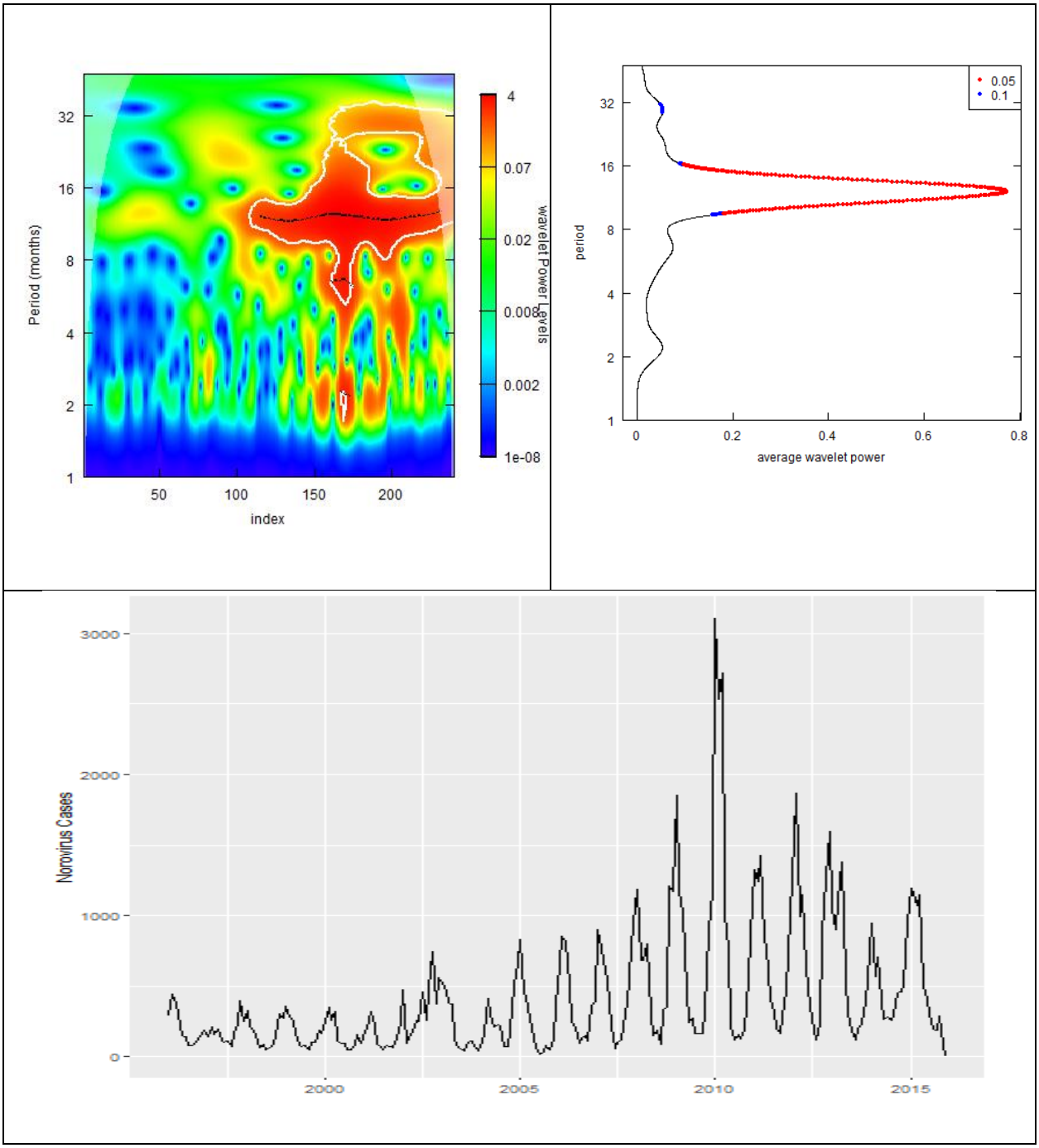


Figure 7 . (7a) Average wavelet power of times series of reported norovirus cases in the United Kingdom from 1996 to 2015. White line represents statistical significance (p = 0.05). Black line represents the ridge of wavelet power highlighting the highest level of power in the spectrum. (7b) Average wavelet plot of time series by period. Significant levels of power are highlighted as red (p = 0.05) and blue (0.01). (7c). Time series for reported norovirus cases in the United Kingdom from 1996 to 2015.

United States

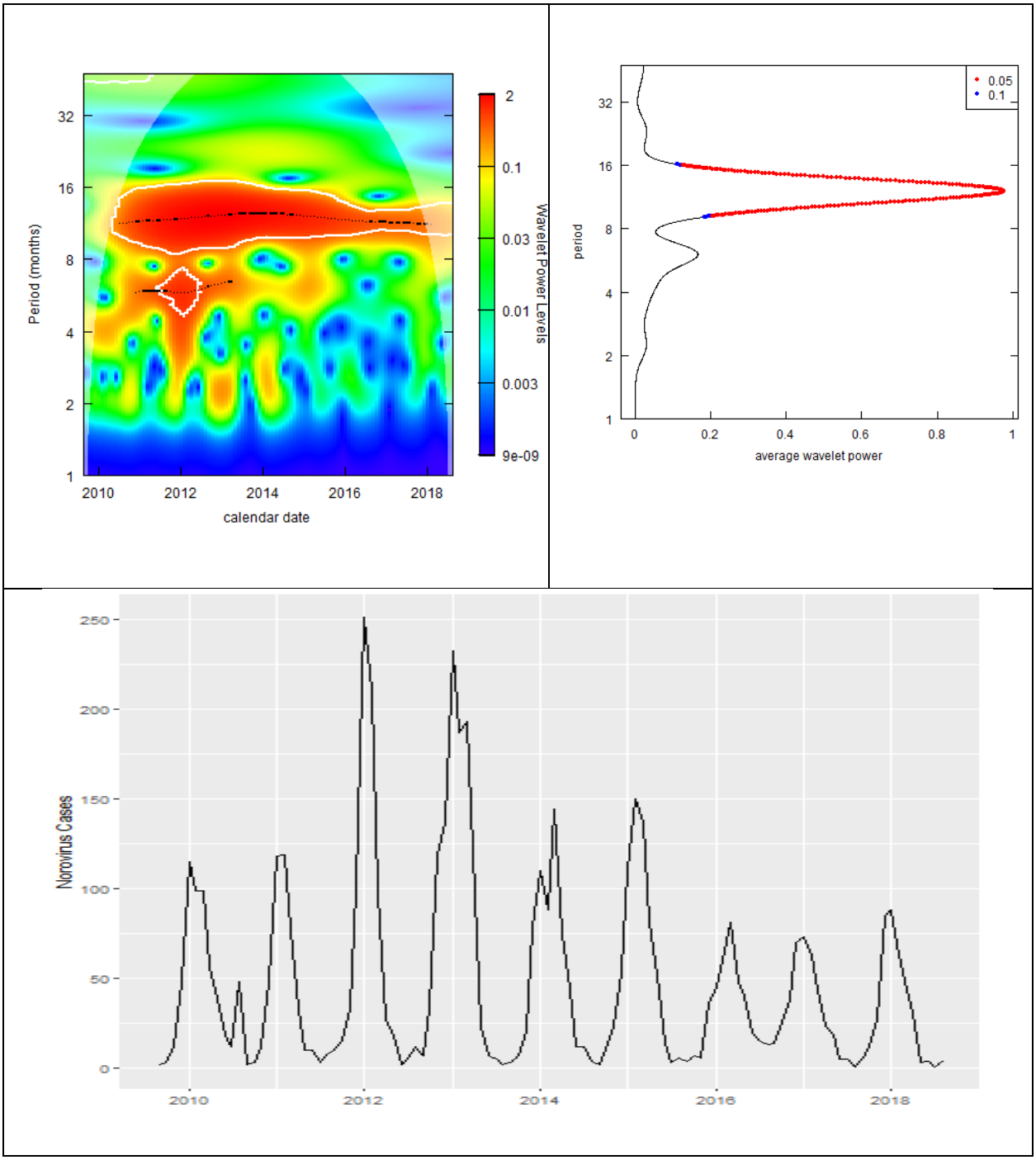


Figure 8. (8a) Average wavelet power of times series of reported norovirus outbreaks in the United States from 2009 to 2018. United States reports norovirus outbreaks, defined as an occurrence of two or more similar illnesses resulting from a common exposure that is either suspected or laboratory-confirmed to be caused by norovirus. White line represents statistical significance (p = 0.05). Black line represents the ridge of wavelet power highlighting the highest level of power in the spectrum. (8b) Average wavelet plot of time series by period. Significant levels of power are highlighted as red (p = 0.05) and blue (0.01). (8c). Time series for reported norovirus outbreaks in the United States from 2009 to 2018.