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Changing Seasonality of Infectious Diarrhea in the Sichuan Province of China from 2005 to 2017

By

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Master of Public Health

Global Epidemiology

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Faculty Thesis Advisor: Benjamin A Lopman, PhD

An abstract of

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

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Abstract

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Many diseases, including infectious diarrhea, follow both secular and seasonal trends in incidence. These trends are crucial to understand for public health interventions, allowing professionals to understand the effectiveness of current techniques and tailor new responses to fit the dynamics of disease. Little is known about the temporal pattern of infectious diarrhea in the Sichuan Province of China. We used data from the National Infectious Disease Reporting System (NIDRS) to evaluate the seasonal and secular trends of infectious diarrhea, categorized as Bacillary Dysentery (BD) and Other Infectious Diarrhea (OID) from 2005 to 2017. Individual case reports were aggregated by month and used to generate time series plots, perform wavelet analyses, and fit negative binomial regression models. The seasonality of OID in Sichuan shifted from a 12-month periodicity with a summer peak from 2005-2013 to a 6-month periodicity with summer and winter peaks from 2013-2017. For BD, there was a nearly 80% decrease in median monthly reported cases from 2,305 in 2005 to 484 in 2017. As the median monthly reported BD cases decreased, the seasonal pattern shifted towards the winter months, potentially indicating a baseline endemicity underneath the seasonality. Firstly, our study concluded that the incidence of BD has greatly reduced, possibly due to recent efforts to improve water and sanitation health in the region. Secondly, we hypothesize the shift in OID seasonality indicates that there has been a change in the makeup of pathogens within the disease categorization.

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Table of Contents

Background

A wide range of infectious diseases including vector-borne, fecal oral, sexually transmitted, and childhood infections follow seasonal patterns (1-4). Many factors contribute to seasonal or other periodic patterns of disease in humans and can be categorized as environmental, pathogen, or host factors (1, 4). Host factors, such as immune response, birth rate, and migration patterns, along with pathogen factors, such as antigenic shifts, affect the host's susceptibility to disease and the pathogen's ability to infect the host; while environmental factors, including humidity, temperature, and vector abundance, change the pathogen's survival in the environment and the host's probability of exposure. (1, 4, 5). While there are many influences on the repetitive changes of disease over time, ultimately it is the interplay between host susceptibility and the transmissibility of the agent on both an individual level and population level that governs the seasonal patterns of infectious disease commonly observed (6, 7).

Seasonality in infectious diarrhea is distinct between viral pathogens, which occur more frequently in colder and drier months, and bacterial pathogens, which occur more frequently in warmer and wetter months (8-11). The seasonality of parasitic causes of diarrhea is not as well studied, although some evidence points towards a winter-time peak (12). The most common viral pathogens that cause diarrhea, norovirus and rotavirus, typically follow a winter and cold month seasonality, however many low-income and/or tropical regions experience year-round disease, possibly due to higher endemic levels of disease and a constant influx of susceptible individuals due to high birth rates (13, 14). The most common bacterial pathogens that cause diarrhea, *shigella* spp, *campylobacter*, and pathogenic *E. Coli*, typically follow a summer and rainy month seasonality, however there are many places where high levels of infection occur year-round due to poor sanitation and health (8, 15-17). The seasonal patterns of bacterial and viral pathogens result from a complex interaction with factors such as humidity, temperature, and salinity, which can have varied effects depending on the pathogen and environment (18). Campylobacter incidence in England has been shown to have consistent peaks in late Spring, with factors such as temperature, prevalence in animals, and human behaviors cited as possible causes (19).

Diarrhea continues to be a leading cause of morbidity and mortality, especially in young children, but steps to reduce the burden have been made (20-22). Diarrhea is the eighth leading cause of death among all ages and the fifth among children under 5 years of age (21). In China in 2015, there were an estimated 418739.7 daily adjusted life years (DALYs) lost due to diarrheal disease, a 58.5% reduction from 2005, and 5851 deaths due to diarrheal disease across all age groups(23). A national study of diarrheal pathogens in China found that rotavirus was the most common diarrheal pathogen, followed by *Shigella*, caliciviruses such as norovirus or sapovirus, diarrheagenic *Escherichia coli*, and *Salmonella* (24). Within China the diarrheal disease burden is greater in rural than in urban areas, particularly in west China where sanitation conditions are typically worse (25). The Chinese government has taken steps to improve water and sanitation health (WASH) and while this has greatly reduced incidence of bacterial diarrhea in urban areas these improvements have yet to be fully implemented in rural areas; additionally, WASH expansion has not had a large effect on viral diarrhea (15, 25-28). Urbanization and improvements in WASH help to prevent diarrhea of bacterial causes but not viral, which is often spread through person-to-person contact and may spread more easily in high density populations (29-31).

Even with the heavy burden of diarrheal disease throughout China, the seasonality of infectious diarrhea is not well understood. Historically, the highest incidence of diarrhea occurs in late summer, which coincides with the peak of bacterial pathogens, while the lowest incidence occurs in early spring, which comes shortly after the winter peak of viral pathogens (24, 25, 32). However, the timing of peak incidence may differ by age, with children under five more likely to have a fall-winter peak, and adolescents and adults displaying a summer peak (33). Additionally, the timing of peak incidence of Bacillary Dysentery may differ between provinces, illustrating that there may be pathogen-specific spatio-temporal differences at the sub-national level (28).

Here we utilize China's real-time national infectious disease reporting system (NIDRS) to investigate the seasonality of infectious diarrhea at the county level within the Sichuan province of China. The dataset, which spans from 2005-2017 and includes records for over 700,000 case reports, allows for the description of seasonal factors, such as length of cycle peak interval intensity, and provides an opportunity to explore how incidence and seasonal patterns are changing over this time period.

Methods

Data Collection

The NIDRS is a passive, real-time surveillance system which collects the mandated case reports from all hospitals and health clinics of any patient presented with symptoms of 39 different diseases (34). Both Bacillary Dysentery (BD), identified by tenesmus symptoms, presence of pus or mucus in the stool, watery stool, or loose stool, and Other Infectious Diarrhea (OID), defined as infectious diarrhea excluding cholera, dysentery, typhoid, and paratyphoid, are class C diseases, require submission of case reports within 24 hours (28, 34). Individual case reports of Typhoid, Paratyphoid, Hepatitis A, Amoebic Dysentery, BD, and OID from 2005 through 2017 in the Sichuan Province of China were received from the China CDC. Other items included in the data are date of birth, age, occupation, district code (GBcode) for patient residence and reporting facility, case severity categorization, lab confirmation status, symptom onset date, diagnosis date, and death date.

Time Series

Time series and seasonality analyses were conducted to assess the presence of both long-term and distinct seasonal trends of BD and OID. Individual case reports dating from January 1, 2005 to December 31, 2017 were aggregated by month for both BD and OID. Time series plots were generated to visually graph the monthly incidence of reported cases over time (Figure 2).

Wavelet Analysis

A wavelet analysis of BD and OID cases was performed to quantify the periodicity of the two time series. The data was first detrended through a simple linear regression to isolate the seasonal trends from the general trend. The residuals were output and further analysis of the wavelet was completed utilizing the "WaveletComp" R package. This package utilizes the Morlet wavelet (35, 36).

Negative Binomial Regression

Regression was used to quantify any long-term trends, to assess the effect of season on expected monthly case counts, and to determine if the effect of season changed over the study period. Preliminary analysis revealed overdispersion in the count data due to the large seasonal variance, thus regression utilizing the negative binomial distribution was used, allowing for adjustment of the dispersion parameter. Two separate negative binomial regression models (Eqn. 1) were fitted for BD and OID, with monthly cases as the dependent variable and utilizing season, year, and the interaction between season and year as independent variables. The predicted monthly case counts were compared to reported data and the residuals were plotted to evaluate model fit and auto-correlation respectively.

Equation 1:

$$y = \beta_1 + \beta_2(\texttt{Spring}) + \ldots + \beta_4(\texttt{Fall}) + \beta_5(\texttt{Year}) + \gamma_1(\texttt{Year}) * (\texttt{Spring}) + \ldots + \gamma_3(\texttt{Year}) * (\texttt{Fall}) + e$$

Results

There were 203,463 reported cases of BD and 466,944 reported cases of OID from 2005 - 2017 in the Sichuan Province of China (Table 1). For BD, there was a nearly 80% reduction in median monthly reported cases from 2,305 in 2005 to 484 in 2017. June and summer season exhibited the highest median monthly reported cases of BD with 1,781 and 1,591 respectively. The median values of reported BD gradually decrease after peaking in 2006 at 2,648, dropping to the lowest count of 484 in 2017 (Figure 1). For OID, there was a nearly 30% reduction in median monthly reported cases from 3,672 in 2005 to 2,969 in 2017 (Table 1). July and summer season exhibited the highest monthly and seasonal median values with 3,961 and 2,834 respectively. The median values slowly decrease after the peak at 4,979 in 2006 but increase in 2016 and 2017 (Figure 1).

Wavelet analysis of the detrended time series for BD revealed a consistent 12-month seasonal period at a peak power level of 3.8, indicating a high and statistically significant amplitude for the 12-month cycle wave pattern (Figure 3a). As the time series progresses, the power level of the periodicity drops but the periodicity does not appear to shift. Wavelet analysis of the detrended time series for OID showed a pronounced 12-month periodicity from 2005 to 2013 (Figure 3b). However, the power level of the 12-month periodicity drops sharply after 2013 and a 6-month periodicity increases in power level after 2013.

For BD we found that, when compared to winter, case counts for months within the summer season are highest (RR = 3.33; 95% CI, 2.72-4.07), followed by months within the fall season (RR = 2.51; 95% CI, 2.05-3.06) and months within the Spring season (RR = 2.17; 95% CI, 1.77-2.66) (Table 2). We also found that there is a secular decrease in monthly case count per year (RR = 0.88; 95% CI, 0.87-0.89), estimating that the case counts in any given month is expected to be 88% that of the same month in the previous year. The interaction terms between season and year, treating winter as the referent, were estimated to contribute to the largest case reduction for months within the fall season (RR = 0.96; 95% CI, 0.93-0.98) followed by summer (RR = 0.97; 95% CI, 0.94-0.99) and spring (RR = 0.98; 95% CI, 0.95-1.00). This indicates that each year the seasonal pattern shifts towards the winter months, illustrated by the below-null estimates for the other seasons.

The OID negative binomial regression model showed that, when compared to winter, months that are within the fall season exhibited the highest case counts (RR = 2.31; 95% CI, 1.89-2.81) followed by summer season (RR = 2.24; 95% CI, 1.84-2.73) and spring season (RR = 1.53; 95% CI, 1.25-1.87) (Table 2). The model showed a slight increase in monthly case count each year (RR = 1.02; 95% CI ,1.00-1.04). The interaction terms between season and year, treating winter as the referent, estimated the greatest reduction of monthly case count for months within the fall (RR = 0.91; 95% CI, 0.89-0.93), and similar reduction for spring (RR = 0.93; 95% CI, 0.91-0.96) and the summer (RR = 0.93; 95% CI, 0.91-0.95). This indicates that each year the seasonal pattern shifts towards the winter months, illustrated by the below-null estimates for the other seasons.

Discussion

We have described the seasonality of reported cases of BD and OID in the Sichuan Province of China from 2005 to 2017 using national surveillance data. The seasonality of OID in Sichuan shifted from a 12-month periodicity with a summer peak from 2005-2013 to a 6-month periodicity with summer and winter peaks from 2013-2017. For BD, there was a nearly 80% decrease in median monthly reported cases from 2,305 in 2005 to 484 in 2017. As the median monthly reported BD cases decreased, the seasonal pattern shifted towards the winter months, potentially indicating a baseline endemicity underneath the seasonality.

The time series analysis, including plotting (Figure 2) and regression modeling (Table 2), showed a significant secular reduction in monthly reported cases of BD throughout the study period. Additionally, we have shown that BD peaks in the summer season and follows a distinct annual pattern. The results of the wavelet analysis showed that this pattern stayed consistent even as reported cases of BD continued to decrease throughout the study period.

While we cannot definitively say, the decrease in BD may be attributable to improved WASH principles, as China has continued to make this a national priority (37, 38). A recent study by Luo et al estimated that the Sichuan Province had one of the highest rates of improved sanitation (39). We observed a nearly 80% decrease in median monthly reported BD cases from 2005-2017 which is well aligned with the previously reported 30% decrease in the national average annual incidence rate from 2004 to 2014 (40).

The results of the OID analysis suggested a consistent incidence with a shifting pattern of seasonality. While we found a statistically significant estimate for an annual increase of OID, the estimate was small in magnitude, implying that total incidence of reported OID remained more or less the same throughout the study period. We observed a distinct late summer and early fall peak incidence from 2005 through 2011 with a clear change in pattern occurring from 2012 through 2017. We attempted to further describe this trend in the wavelet and regression analyses. Taken together with the results of our regression, this presents a compelling case for a shift towards a biannual peak in incidence in summer and winter. Our three analyses highlight a consistent finding of a shift from a distinct 12-month periodicity from 2005 through 2012 to a 6-month periodicity beginning in 2013 and continuing through the study period. Because no independent variables other than time were considered, our findings may only be used to describe the pattern of seasonality, not to attribute causality. However, external research may be used to attempt to explain the patterns described.

The time series plot for OID not only showed a shift in periodicity, but also displayed sharper peaks and troughs after 2013 than earlier in the study period. We propose that, as the background incidence of bacterial diarrhea decreased, the pattern of viral or other causes of diarrhea became unmasked. So, while it seems that the pattern changed, it may be the case that there are truly two consistent seasonal patterns presented in the OID categorization. As one pattern has decreased in intensity over time, the second pattern is being revealed from behind the noise.

In the time series for both BD and OID there is a large spike in mid to late 2006. This spike may correspond with the emergence of two new GII.4 Norovirus variants that sparked a global increase in Norovirus associated gastroenteritis (41). While this contradicts the common perception that Norovirus is associated with winter time peaks, there are other factors, such as antigenic shift, that may lead to peaks outside of typical seasonality (42). These peaks extraneous to seasonality are often due to a large population of susceptible individuals, who may not have immunity to a new viral strain after a shift occurs, becoming exposed and quickly spreading the virus to those around them.

Our study utilized passive surveillance data which introduces some limitations. First, because the NIDRS is passive, we expect there is an underreporting of disease, thus our estimates may be low. Because our study sought to describe seasonality of the time series, time-dependent biases are of particular concern. The system, which initially received reports by paper, ceased accepting paper forms and mandated digital reporting of cases over the internet in 2004. Use of cell-phone-based reporting was integrated in 2008 in an effort to extend access to remote locations (43). It is possible but unlikely that either of these changes had a noticeable effect on the time series, as computer-based internet reporting through dial-up or broadband internet has been in place in all townships in the Sichuan province since 2004, and there was no obvious step-change in 2008 (43). An additional limitation is the design of the OID categorization in the NIDRS. In the system, OID serves as a “catch-all” categorization for infectious diarrhea that either did not fit the BD definition or did not have a clear pathogen diagnosis. Due to this, OID likely contains cases of diarrhea caused by a variety of pathogens including both bacterial and viral. We may further postulate that the summer and winter peaks revealed in OID may be caused by bacterial and viral pathogens respectively, as it has been shown that in

China both classes of pathogen follow the expected seasonal trend (33). This would indicate that while bacteria caused diarrhea has decreased in incidence due to improvements in WASH principles, shown by the reduction of the summer peak, diarrhea caused by viruses has remained constant or even increased, as evidenced by the rising winter peak. This would not be a surprising finding, as it has been shown repeatedly that, while urbanization and improvements in WASH help to prevent diarrhea of bacterial causes, WASH improvements are far less effective against viral pathogens and urbanization can lead to increased incidence of viral diarrhea likely due to increased person-to-person interaction (29-31).

Our analysis has described the seasonal pattern of case reports collected by the NIDRS in the Sichuan Province of China from 2005 to 2017 of individuals diagnosed as having bacillary dysentery and other infectious diarrhea. While we believe our analysis is representative of the true seasonal trends, we are limited simply to describing the pattern rather than inferring causal factors or true population incidence and prevalence. Here two major questions remain. The first is what factors, environmental, pathogenic, or otherwise, are leading to the change in seasonality pattern for OID. While we have hypothesized that this shift may be due to the reduction of bacterial causes of diarrhea and an unmasking of viral, our study does not provide ample evidence to prove this. Further studies would benefit from more detailed diagnostic data regarding the pathogens that may cause the symptoms of cases reported into the OID category. The NIDRS does not currently collect detailed diagnostic data. The second unanswered question is how the described seasonal patterns change spatially within the province. Sichuan contains both urban and rural environments which are known to experience different patterns of disease. Each case report within the NIDRS data is identified with the clinic or hospital where the patient was reported. This information, combined with population density or similar data, could be used to differentiate the disease patterns of urban versus rural Sichuan.

Our findings have important public health implications for the control of infectious diarrhea in Sichuan. Firstly, it is important to accrue evidence that current efforts have greatly reduced incidence of BD, but not eliminated it. Thus, changes must be made to current protocol and new interventions must be put in place if further reduction is to be obtained. Secondly, the clear shift in OID seasonality indicates that something has changed either in the surveillance system or in the makeup of pathogens causing the disease categorization. Our findings suggest that the remaining burden is viral and control measures such as rotavirus vaccination should be targeted accordingly.

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Tables

Table 1. Summary statistics for monthly reported incidence of Bacillary Dysentery and Other Infectious Diarrhea in China, from 2005-2017[a]

	Monthly Reported Cases of Dysentery, Bacillary			Monthly Reported Cases of Other Infectious Diarrhea[b]		
	Median	25th	75th	Median	25th	75th
Month						
January	659	363	862	2,321	2,109	2,432
February	619	383	879	1,827	1,715	2,074
March	859	481	1,259	2,283	2,149	2,354
April	1,049	661	1,690	2,335	1,873	2,747
May	1,600	832	2,479	2,990	2,396	3,826
June	1,781	873	2,661	3,333	2,829	4,231
July	1,591	919	2,537	3,961	2,963	4,211
August	1,548	841	2,375	3,671	3,228	4,306
September	1,263	764	2,081	3,538	2,498	3,878
October	1,003	686	1,800	3,112	2,197	3,765
November	803	482	1,288	3,302	2,283	3,641
December	714	387	978	3,430	3,280	3,637
Season						
Winter (Dec-Feb)	621	381	921	2,411	1,948	3,323
Spring (Mar-May)	1,049	701	1,687	2,354	1,983	2,767
Summer (Jun-Aug)	1,591	857	2,599	3,671	2,834	4,269
Fall (Sep-Nov)	998	646	1,891	3,302	2,273	3,741
Year						
2005	2,305	1,359	3,528	3,672	2,393	4,080
2006	2,648	1,594	3,698	3,952	2,674	4,979
2007	1,965	1,264	2,664	3,852	2,937	4,181
2008	1,671	1,103	2,401	3,723	2,717	3,979
2009	1,574	968	2,004	3,071	2,658	3,682
2010	1,356	918	1,990	3,317	2,254	3,826
2011	1,026	781	1,559	3,501	2,497	3,689
2012	885	650	1,283	2,896	2,332	3,142
2013	805	565	1,048	2,341	2,185	2,819
2014	674	443	834	2,120	1,777	2,265
2015	550	394	676	2,234	1,881	2,361
2016	494	337	689	2,324	1,906	2,750
2017	484	330	688	2,969	2,389	3,658

[a]Only cases reported to the National Infectious Disease Reporting System were elligible

[b]Defined as infectious diarrhea excluding cholera, dysentery, typhoid, and paratyphoid

Table 2. Exponentiated Estimates, 95% Confidence Intervals, and P-values of the Negative Binomial Regressions for Dysentery and Other Infectious Diarrhea

	Dysentery Model			Other Infectious Diarrhea Model		
	Estimate	95% CI	P-Value	Estimate	95% CI	P-Value
Season						
Winter (Dec-Feb)	Referent	-	-	Referent	-	-
Spring (Mar-May)	2.17	(1.77, 2.66)	<0.001	1.53	(1.25, 1.87)	<0.001
Summer (Jun-Aug	3.33	(2.72, 4.07)	<0.001	2.24	(1.84, 2.73)	<0.001
Fall (Sep-Nov)	2.51	(2.05, 3.06)	<0.001	2.31	(1.89, 2.81)	<0.001
Year	0.88	(0.87, 0.90)	<0.001	1.02	(1.00, 1.04)	0.017
Season-Year Interaction						
Winter (Dec-Feb)	Referent	-	-	Referent	-	-
Spring (Mar-May)	0.98	(0.95, 1.00)	0.081	0.93	(0.91, 0.96)	<0.001
Summer (Jun-Aug	0.97	(0.94, 0.99)	0.010	0.93	(0.91, 0.95)	<0.001
Fall (Sep-Nov)	0.96	(0.93, 0.98)	<0.001	0.91	(0.89, 0.93)	<0.001

Figures

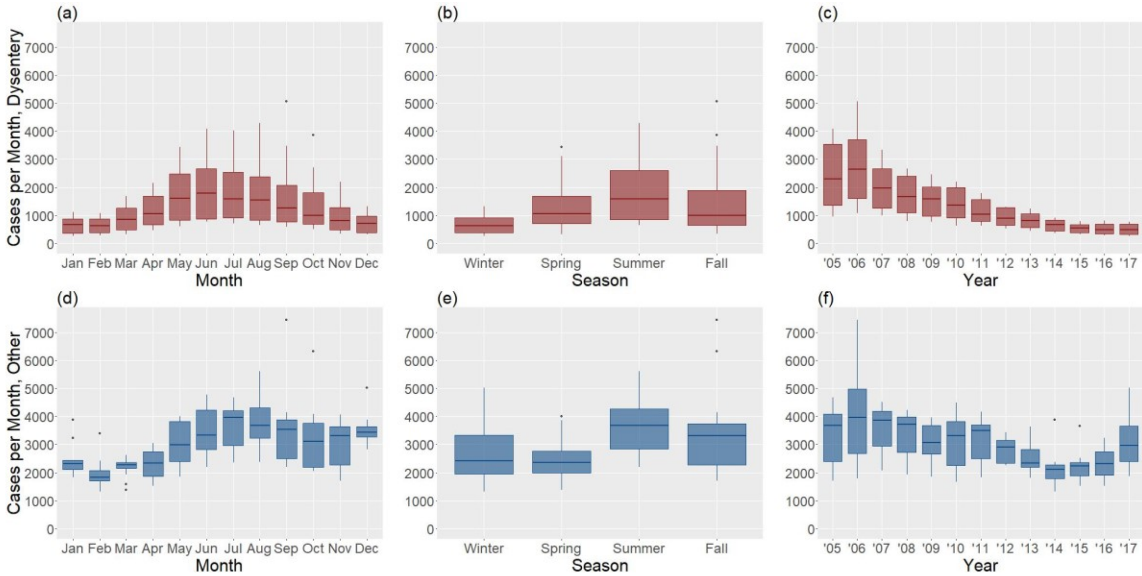

Figure 1. The distribution of monthly reported incidence of BD (red) across month (a), season (b), and year (c), and OID (blue) across month (d), season (e), and year (f) in Sichuan China from 2005-2017. BD identified by tenesmus symptoms, presence of pus or mucus in the stool, watery stool, or loose stool. OID defined as any infectious diarrhea excluding cholera, dysentery, typhoid, and paratyphoid. Seasons defined as winter (December – February), spring (March – May), summer (June – August), and fall (September – November).

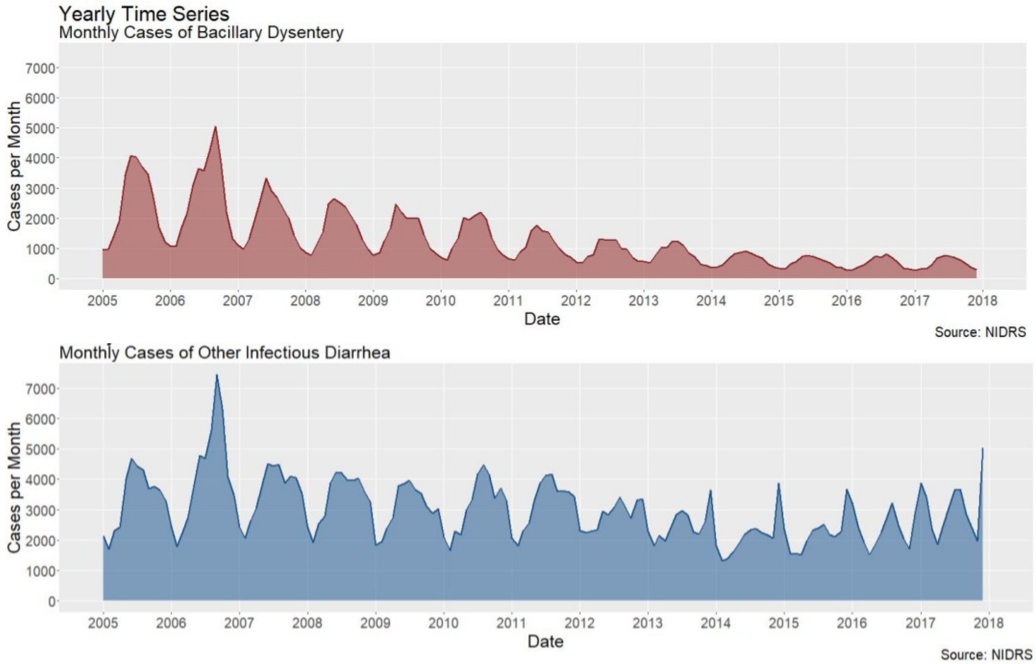

Figure 2. Time series plots of monthly reported incidence of BD (red) and OID (blue) in Sichuan China from 2005-2017. BD identified by tenesmus symptoms, presence of pus or mucus in the stool, watery stool, or loose stool. OID defined as any infectious diarrhea excluding cholera, dysentery, typhoid, and paratyphoid.

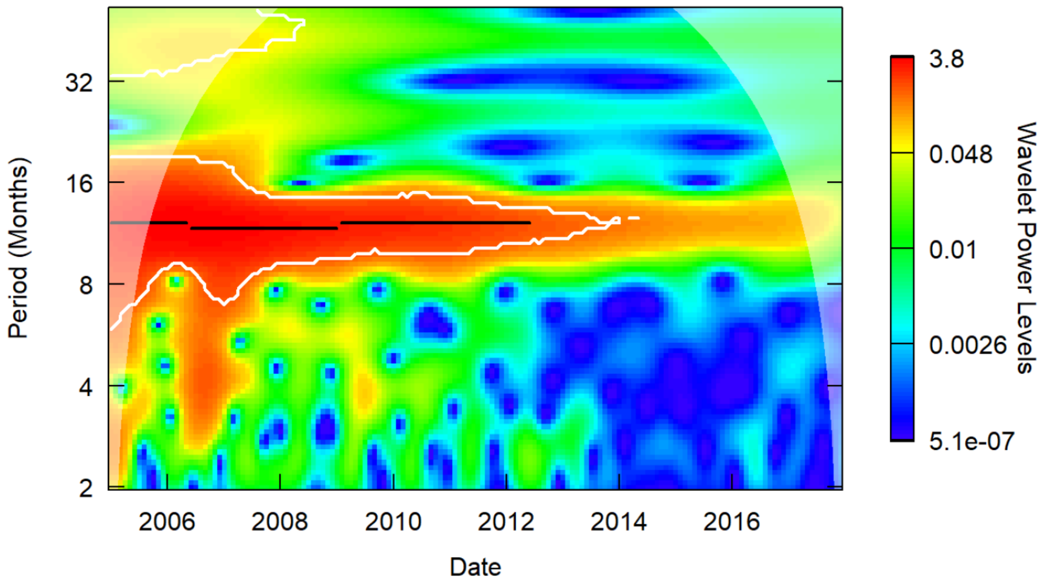

Figure 3a. Average wavelet power of the time series of reported incidence of BD in Sichuan China from 2005-2017. White line indicates statistical significance. Black line highlights the ridge of the wavelet power, indicating the highest level of power in the spectrum.

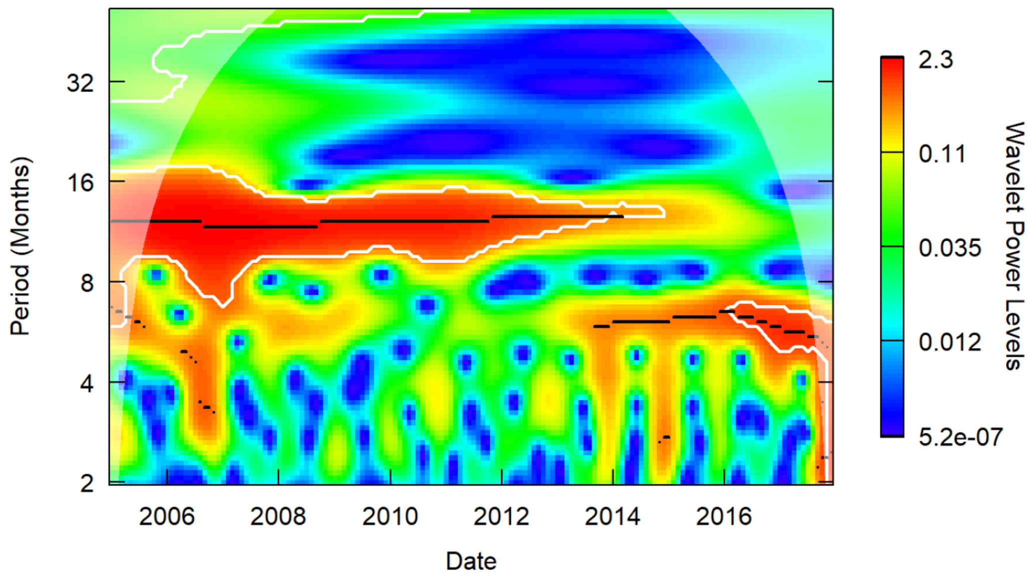

Figure 3b. Average wavelet power of the time series of reported incidence of OID in Sichuan China from 2005-2017. White line indicates statistical significance. Black line highlights the ridge of the wavelet power, indicating the highest level of power in the spectrum.