An Examination of Epidemiologic Patterns of Acute Gastroenteritis
and Potential Risk Factors in a Leisure Setting

By

Jillian Cordes
Master of Public Health
Hubert Department of Global Health

____
Dr. Christine Moe
Committee Chair

An Examination of Epidemiologic Patterns of Acute Gastroenteritis
and Potential Risk Factors in a Leisure Setting

By

Jillian Cordes
B.A., Economics
Northwestern University, 2014

Thesis Committee Chair: Dr. Christine Moe, Ph.D

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
The Hubert Department of Global Health

April 2016

Abstract

An Examination of Epidemiologic Patterns of Acute Gastroenteritis
and Potential Risk Factors in a Leisure Setting

By Jillian Cordes

Background
Travel-associated enteric infections, including traveller's diarrhea and acute gastroenteritis (AGE), are not an uncommon occurrence for travelers. Research on risks factors for AGE in hotel, resort, and cruise ship settings could help guide recommendations to prevent further endemic and epidemic cases.

Objective
The goal of this analysis was to examine epidemiologic patterns of AGE and identify potential risk factors in 22 resorts across the globe owned by one company.

Methods
The study population included 4,739 cases of AGE, out of the 475,875 guests and approximately 23,524 staff at 22 resorts in 2015. In order to compare risk factors by time, duration of resort visits were classified into short and long stays (1-5 and 6-15 days, respectively). An unpaired t-test was used to compare the difference in attack rates between short and long stays at each resort. Linear regression was performed to examine the association between attack rate and potential risk factors.

Results
Although no outbreaks of AGE occurred in the study population, one of the main findings from this analysis was that guests at the resorts had a higher AGE attack rate than staff. (β=0.00149, p-value=<0.0001 for short stays and β=0.00109, p-value=0.0006 for long stays). Another major finding was a positive association between the day of symptom onset and the attack rate during long stays, meaning attack rates increased over the span of a travel package (β=0.00014, p-value=<0.0001). There was an overall higher percentage of cases and attack rate associated with summer.

Conclusion and Recommendations
Further research is needed to improve characterization of epidemiologic patterns of AGE in leisure settings. Advances in testing of norovirus diagnostics and improved identification of cases are top priorities. Recommended research opportunities specific to leisure settings include closer tracking of guest and staff hygienic practices and daily activities. Through increased research and implementation of evidence-based recommendations, resort settings can become a healthier environment for guests and staff.

Acknowledgments

I am incredibly grateful for the assistance throughout the thesis process. First, I would like to thank the resort company for providing me with the data sources and answering my questions along the way. Most importantly, I would like express my gratitude towards Dr. Moe for being my thesis advisor and providing me with constructive feedback and guidance throughout the process. Also, for stretching her already full day to make sure I met all my deadlines. Finally, thank you to Dr. Kirby for being available to me as a second opinion and helping me connect with the resort company.

I would also like to thank my family and friends. Thank you to my fellow soon-to-be MPH graduate mother for all the academic assistance over the years and to my father for supporting my decision to attend Emory. Thank you Lacey Loomer for your all your thesis expertise and allowing me to ask you questions and to Hayley Braun for joining me on my sometimes-lengthy study breaks as well as for offering her computer expertise.

Thank you

An Examination of Epidemiologic Patterns of Acute Gastroenteritis
and Potential Risk Factors in a Leisure Setting

By

Jillian Cordes
B.A., Economics
Northwestern University, 2014

Thesis Committee Chair: Dr. Christine Moe, Ph.D

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 the Hubert Department of Global Health

April 2016

Table of Contents

Chapter 1: Introduction and Literature Review

A. Introduction and Rationale

When traveling, vacationers may find themselves in close quarters with other individuals who may be ill or they may be exposed to enteric pathogens through ingestion of food or water, situations that may lead to enteric infections. Travel-associated enteric infections, including traveller's diarrhea and acute gastroenteritis (AGE), are not an uncommon occurrence for international travelers. Current rates of traveler's diarrhea for a two-week trip abroad range from 10-40% depending on the destination (high-income countries typically have lower rates) [1]. Traveler's diarrhea and AGE may be due to new exposures to new pathogens in a new environment. The case definition for AGE often used in studies of travel-associated enteric illness is: " ≥ 3 loose stools in 24 h, vomiting ≥ 3 times in 24 h, loose stools with two additional symptoms or vomiting with two additional symptoms. Additional symptoms include nausea, fever, abdominal pain, abdominal cramps, and blood or mucus in stool" [2]. This broad case definition encompasses infections by a number of enteric pathogens that cause the same symptoms.

Cases of AGE can often be assumed to be norovirus infections, depending on the context and the symptoms. Highly contagious, norovirus can be spread by an infected person, fecal-contaminated food or water, or by contact with a fecal-contaminated surface [3]. Cases of norovirus can occur in people of all ages [3]. Symptoms of norovirus typically include stomach pain, diarrhea, vomiting, and nausea. Children under the age of one year typically experience diarrhea as the main symptom of norovirus, while those above the age of one predominately demonstrate nausea and vomiting [4]. The virus is most commonly transmitted through the fecal-oral route and contamination of shared restrooms [5-7]. Annually, norovirus is estimated to cause about 19-21 million cases of AGE within the United States as well as 56,000-71,000 hospitalizations and 570-800 deaths [3]. Deaths are most common amongst those under 5 and the elderly, both of whom have more trouble maintaining hydration [8]. Commonly referred to as “stomach flu” or “food poisoning,” norovirus is the leading cause of illness and outbreaks from contaminated food in the United States [3]. The onset of symptoms typically occurs 12-48 hours after exposure, and the illness lasts 1-3 days [9]. One can be infected with norovirus more than once in a lifetime due to different types of the virus [9]. Contagion levels peak during the symptomatic phase and the first few days after the illness, and the virus may be excreted in feces for up to two weeks after symptoms resolve [9].

Norovirus can be diagnosed in a clinical laboratory setting. The most common diagnostic assay is real-time reverse transcriptase-polymerase chain reaction (RT-qPCR). The assay detects the genetic material of the virus in stool, vomit, or environmental specimens. Another method includes use of an enzyme immunoassay (EIA) for detection of a virus antigen in stool samples, but this technique lacks sensitivity to diagnose an individual case. Health departments are currently not required to report individual cases of norovirus, and typically only outbreaks lead to reported diagnoses. [10]. Due to the difficulties in testing each case for norovirus, cases are often reported as AGE. There is limited research on the prevalence of norovirus in travellers’ diarrhea, but norovirus is known to be the leading cause of AGE cases amongst all age groups in the United States [11, 12].

Currently, there are no antiviral treatments for norovirus. Recommendations for norovirus treatment include maintaining hydration through the use of oral rehydration solutions and preventing further transmission by avoiding contact with others [13]. Prevention of norovirus relies heavily on hand washing and the proper preparation of foods. Hand washing should occur after using the toilet and before eating, handling, or preparing food. Fruits, vegetables, and shellfish are particularly susceptible to norovirus [14]. Norovirus is also resistant to temperatures up to 140 degrees Fahrenheit, and so steaming shellfish does not eliminate the virus [14]. Chlorine bleach or another EPA certified disinfectant should be used to clean areas soiled with vomit, and contaminated clothing or linens should be immediately washed [14].

Epidemic and endemic AGE can have high direct and indirect costs. Costs-of-illness estimates are calculated as "the sum of 1. the cost of treating illness, 2. the value of time that cannot be spent on other valued activities because the individual is ill, 3. the pain and suffering involved with the illness, 4. expenditures on avoiding the illness, and 5. in some cases, the pain and suffering the illness causes others, particularly family members" [15]. The calculation uses estimates from the U.S. Centers for Disease Control and Prevention (CDC) on disease incidence and hospitalization information was taken from the Nationwide Inpatient Sample (NIS) [15]. Lost productivity is measured as time taken away from work and uses the average daily wage rate, adjusted for unemployment[15]. Costs to avoid the illness are related to the Value of a Statistical Life, which measures one's willingness to pay to reduce the risk of death [15]. In 2013, the economic burden of norovirus was calculated as $2,255,827,318 in 2013 dollars [15]. Due to this high burden, investment should be made into norovirus prevention.

B. Problem Statement

There is a lack of data characterizing endemic AGE in leisure settings. Most information about AGE among travelers comes from outbreak investigations. AGE outbreaks are common in leisure settings (such as a hotel, resort, or cruise) where there are large concentrations of people in confined areas and pathogens can spread quickly [9]. These outbreaks pose a significant public health risk to the exposed population and can be costly and disruptive to the leisure setting and the traveler. Research on risks factors for AGE in hotel, resort, and cruise ship settings could help guide recommendations to prevent further endemic and epidemic cases.

C. Literature Review

AGE is common amongst travelers vacationing in leisure settings, and much of our understanding of AGE risks in these settings come from outbreak investigations [16]. These outbreaks investigations include hotels, resorts, and cruise ships across the world, and the outbreaks can be classified by transmission route, including water, food, person-to-person contact, and fomites in the environment. Often an outbreak may start from a point source vehicle, such as contaminated water or food, or by a common exposure event such as an ill guest vomiting in a public space, but then the outbreak often continues to spread through a combination of transmission routes.

Waterborne Outbreaks in Leisure Settings

Within a resort setting, guests often use the same source of drinking water, and some resorts may have their own water supply rather than a municipal water supply. In situations where this source contains fecal contamination, norovirus outbreaks can occur with a high attack rate. In 1989, approximately 900 guests in a resort in Arizona developed norovirus from drinking tap water from the resort well. In order to prevent further outbreaks, use of the well was limited to irrigation purposes, and the resort was connected to a community water source that would be chlorinated and monitored [17]. After the new water source was connected, there were no major outbreaks in the resort.

In 1998, an outbreak in a resort in Bermuda led to at least 448 guests and staff members with AGE symptoms. Water samples from the resort's tank and various potable water sites within the hotel were sent to the CDC to be tested for coliform bacteria and viruses. The microbiological analyses indicated that 9 of the 10 samples had fecal contamination. It was assumed that this contamination led to the AGE cases, and 18 of the 19 stool samples collected from those with AGE symptoms were positive for norovirus. This led to the source of the outbreak being identified as the water supply and a call for the regular inspection and monitoring of water supplies in resort settings. Chlorination of supplemental drinking supplies and measures to prevent food outbreaks were also recommended to help prevent these outbreaks. Prevention methods such as these are particularly important in tourist-dependent nations such as Bermuda. Upon reopening, guests were initially provided with purified bottled water to drink, and there were no more reported norovirus outbreaks [18].

In 2000, there was an outbreak in a hotel southern Italy where 334 AGE cases were identified within the month of July, and 20% of the cases were in staff members. Guests who became ill typically had symptoms a few days after arrival, and the attack rate in the first week was 10.5%, 8.7% for week 2, and 10.1% in week 3. Showering on the beach and consuming drinks with ice were associated with the highest relative risk amongst staff members. This outbreak was also attributed to a contaminated water source that was found to have fecal bacteria. Control measures included banning the consumption of tap water, and bottled water was provided for drinking and washing vegetables. The same water source was still used for showering and ice production, the measures had no effect on controlling the outbreak, likely because they did not address the point source and did not prevent person-to-person contamination [19].

Another outbreak occurred in a resort in central Italy in 2003, and 183 cases were identified. Those with symptoms were significantly more likely to have swum in the sea and have used common showers and certain sanitation facilities in the resort. The outbreak was linked to the positive identification of norovirus in groundwater. The water line was cleaned and routinely maintained, and a water quality surveillance plan was implemented. Additionally, standard operating procedures were prepared for the management of norovirus infections. Since these measures were taken, there have been no more reported epidemics in the resort [20].

There are a number of reports in the scientific literature of norovirus outbreaks in leisure settings that started from a contaminated groundwater source. Once in the water, norovirus is able to infect guests and staff due to poor or no water quality surveillance. In all of these reported outbreaks, when the water source was targeted and treated, the outbreaks ended. Having strict regulations for water treatment and monitoring is an effective way to prevent outbreaks of norovirus from groundwater.

Outbreaks in Leisure Settings Associated with Environment Contamination or Person-to-Person Transmission

Disease transmission via person-to-person contact or contact with environmental contamination can be more difficult to control than groundwater source outbreaks. Isolation of cases can be challenging to enforce, and encouraging handwashing may be insufficient to control an outbreak. The best control measure for outbreaks spreading by person-to-person transmission or environmental contamination was a temporary shutdown of the resort, followed by extensive cleaning.

In 2007, an outbreak of norovirus in the Dominican Republic led to a resort being temporary closed down. Over 800 people were affected within 15 days in July. Environmental samples, including water samples from pipes, tanks, and swimming pools, and surfaces, were tested for norovirus using the RT-qPCR technique. Although the results were negative, risky foods, such as salads and seafood, were removed from the menu, and the water was hyper-chlorinated. Surfaces were also cleaned and disinfected, but cases continued to rise. It was concluded that an ill guest introduced the virus into the resort and that the virus was transmitted via environmental contamination from vomiting or diarrhea. Interventions to prevent further transmission, including extra cleaning of toilets and mandatory handwashing before dining, were not sufficient to control the outbreak until the resort suspended entry of guests [21].

An outbreak in a hotel in England in 1996 caused the hotel to shutdown for a week. Of the 4,291 guests of the hotel from January 15 to March 15, 850 developed symptoms of norovirus. Many of the guests were elderly and unable to reach the toilet before vomiting. After reopening in the end of March, cases increased again and finally subsided at the end of June. While closed, surfaces were cleaned with water and detergents, but not disinfectants due to concern that carpets would be damaged. The possibility of food contamination was examined by investigating kitchen hygiene and guests' food history, and no association was found. Environmental samplings was conducted by collecting swabs from surfaces including carpet, toilets, door handles, and cushions. Samples positive for norovirus included five from the carpet and one from a toilet rim. These results indicate that the most likely route of transmission was contact with contaminated fomites and the surface cleaning was inadequate to eliminate the virus [22].

Infected cases can spread norovirus via physical contact with their surroundings and vomit can contaminate surface areas. Contaminated fomites can be difficult to identify and clean, but with the proper cleaning materials and thorough cleaning, further cases can be prevented.

A property insurance firm developed a manual to assist managers in the hospitality industry in preventing and controlling norovirus and other AGE outbreaks [23]. The manual emphasized economic costs that could result from an outbreak. It states that "a norovirus outbreak can lead to significant expense because the property may have to be shut down to undergo extensive cleaning. Business interruption costs and possible bodily injury claims also have to be considered along with workers' compensation claims from sickened employees" [23]. Taking proper precautions can not only keep guests healthy, but also protect their own business. An outbreak can increase costs and reduce income, and it is in the industry's best interest to invest in the correct health precautions.

AGE Outbreaks on Cruise Ships

Cruise ship settings have a reputation for norovirus outbreaks. Although a study on self-reported cases of upset stomachs found that cruise ships actually have lower percentage of guests reporting upset stomachs than land-based leisure settings (4.8% vs. 7.2%, respectively), norovirus outbreaks on ships are more difficult to contain once they begin [1, 24]. Norovirus has no vaccine or direct treatment; therefore, it is crucial that cruise ships take all necessary steps to reduce the transmission of norovirus. The Centers for Disease Control and Prevention (CDC) created the Vessel Sanitation Program (VSP) in 1975 to provide information to cruise lines regarding public health practices that will help keep their crew and passengers as healthy as possible [25, 26]. VSP also conducts sanitation and food safety inspections of the cruise lines as well as continuous surveillance and outbreak investigation of acute AGE [25]. The reported case definition for AGE is "three or more episodes of loose stools in a 24 hours period" or "vomiting and one additional symptom including one or more episodes of loose stools in a 24-hour period, or abdominal cramps, or headache, or muscle aches, or fever (temperature of ≥100.4°F) [25]. The VSP recommends passengers with these symptoms remain in their room for at least 24 hours after symptoms' end and to follow-up with infirmary personnel. A defined outbreak occurs when over three percent of the crew or passengers report AGE to the ship's infirmary, and this may result in a CDC investigation [27].

According to the CDC, “Since implementation of the cooperative program between the cruise industry and VSP, the outbreak rate on vessels each year has steadily declined” [25]. From 2008 to 2014, the CDC reported that of the 74 million American cruise line passengers, there were 129,678 AGE illnesses reported, accounting for 0.18% of all passengers and 0.15% of crew. Among the cases clinically tested, 92% were caused by norovirus and *E. coli* was the second most common agent [28]. Within this period, cases decreased from 27.2 per 100,000 travel days to 22.3 [26].

An outbreak of norovirus on a cruise ship in 2002, led to an investigation of the mode of virus transmission onboard. The study began a week after 84 passengers of 2,318 (4%) presented symptoms. After two cohorts of passengers and the outbreak continued, the ship was shut down for cleaning, but the outbreak continued when the next cruise began. The study found that passengers eating at a particular restaurant were more likely to develop the virus within the first few days, and by day five, those sharing a cabin with sick passengers were most at risk. The epidemiologic analysis pointed to a food source as the original source of outbreak, after which transmission continued via person-to-person and environmental contamination. It was hypothesized that either the cleaning of the ship was not adequate to remove the virus or an ill staff member returned to work after the cleaning and re-contaminated the ship. Recommendations from the study include that efforts to control outbreaks address all pathways of transmission; ill crew members should be offered paid sick leave; and symptomatic guests prior to arrival should be incentivized to postpone their trip [29].

When the source of the outbreaks can be identified, norovirus outbreaks associated with food are the easiest to remedy. Testing of the food or studying eating patterns can assist in detection. Once the food has been identified, disposal of the contaminated food and improving preparation methods can prevent further illness.

A 2009 retrospective cohort study of a suspected norovirus outbreak on a cruise ship found that during the outbreak, there was increased awareness of the virus and a stronger emphasis on hand washing. The study conducted surveys about hygienic practices and possible norovirus exposure. Stool samples were also collected and tested by RT-qPCR to confirm cases, and the main source of transmission was thought to be person-to-person. Despite the cruise line's recommendations, relatively few ill passengers decreased their activities [27]. Ill passengers reported participating in fewer activities than those who were not ill, but it is unknown if this was because they were feeling ill or because of the medical staff's recommendation [27]. The study suggested having incentives for sick passengers to voluntarily self-isolate. There should also be incentives for passengers to seek medical care as soon as they experience symptoms. Of established cases, 40% did not report their illness to the infirmary. The study also found that crewmembers might be hesitant to report an illness if they did not wish to miss work [27]. Although crew and passengers were being provided with information to prevent and control norovirus illness, there needs to be extra motivation for them to adhere to the recommendations.

A study published in 2006 on the epidemiology of AGE on cruise ships from 2001-2004 confirmed an association between developing illness and sharing bathrooms with ill passengers that have been vomiting [30]. Although peaks for norovirus among the general American population occur during the winter months, the study found that norovirus on cruise ships is most common during summer months, the most popular time to vacation [30]. Key recommendations from the study were to isolate sick passengers and thoroughly clean the ship during the summer months. The European Manual for Hygiene Standards and Communicable Disease Surveillance on Passenger Ships is a manual developed by the European Union-funded EU SHIPSAN project. It recommends actions to prevent maritime health threats in the European Union, and found that the risk of norovirus is exacerbated when a cruise ship travels internationally, due to in part to different hygienic standards and disease surveillance practices [31].

Person-to-person transmission can be particularly difficult to control on a cruise ship. Compared to hotel and resort settings, cruise ships are typically more confined. Along with the temporary shutdown of a cruise during an outbreak, encouraging isolation and the reporting of illness can be effective measures to reduce person-to-person transmission.

Overall, the numbers of reported AGE outbreaks in leisure settings appears to be declining over time. Outbreak investigations that were able to test stool specimens in a laboratory and determine the etiology of the outbreak had a better opportunity to control outbreak. By understanding the cause of the outbreak, proper prevention and control techniques specific to the transmission route can be implemented. For example, knowing the source is waterborne can lead to improved treatment of drinking water at a resort. The most effective method for outbreak control was closure of the resort or vessel. However, this is not always feasible or economical. In order to improve AGE prevention, there is a need for more information regarding the pathways for transmission and the factors that affect AGE attack rates. In many reports, the investigations were inconclusive about the source of the outbreak or unable to control them. Building on existing literature, this analysis of reported AGE cases in leisure settings will provide additional insights into the epidemiology of AGE transmission, risk factors, and the population affected in leisure settings.

E. Purpose Statement

The goal of this analysis was to examine epidemiologic patterns of AGE and identify potential risk factors within a leisure setting. The results of the analysis can inform management in the leisure industry on where to focus their efforts to protect clients against AGE and better understand risk factors within their settings.

F. Research Questions

The following research questions examining patterns of AGE cases by person, resort, seasonality, time, and place were addressed:

Question 1: Are there differences in the attack rates for guests and staff?

Null hypothesis: There are no differences in the attack rates by guests and staff.

Question 2: Does the attack rate vary by resort?

Null hypothesis: The specific resort does not impact the attack rate.

Question 3: Does the size of the resort impact the attack rate?

Null hypothesis: The size of the resort does not impact the attack rate.

Question 4: Are there differences in attack rate depending on the month or season?

Null hypothesis: There are no differences in attack rate depending on the month, quarter, or season.

Question 5: Does the length of the stay impact the attack rate?

Null hypothesis: The length of stay does not impact the attack rate

Question 6: Does the timing of symptom onset relative to the start of the travel package impact the attack rate?

Null hypothesis: The timing of symptom onset relative to the travel package does not impact the attack rate.

Question 7: Does a delay in case reporting impact the attack rate during a specific cohort of travelers?

Null hypothesis: A delay in reporting does not impact the attack rate during a specific cohort of travelers.

Question 8: Does the distance from the guest and staff assigned rooms (approximated by floor in the resort) to the dining hall used by guest or staff impact the attack rate?

Null hypothesis: The distance from the guests' floor to the dining hall does not impact the attack rate.

G. Significance Statement

Leisure settings, such as hotels, resorts, and cruise ships, often have a reputation for high incidence of AGE. By examining patterns and risk factors for AGE, evidence-based guidance can be offered to all resorts on how to best prevent and control AGE in this setting. There can be significant economic benefits from protecting the health of guests and staff in leisure settings. A safer environment may boost guest numbers and increase resort revenue. Less illness at the resort would require less expenditure on managing outbreaks, including cleanup costs. There would also be less staff absenteeism and a higher reputation for the resort. Health costs would also be expected to decrease, lowering the burden placed on individuals and insurance companies.

Chapter 2: Methods

A: Definition of Terms

In this analysis, "resorts" are defined as any recreational setting such as a hotel or cruise involving guests visiting with the intention to enjoy themselves. The terminology "staff members" is used to represent anyone directly hired by the resort to work in the resort space. "Guests" refer to any paying visitor to the resort setting. The "attack rate" was calculated as the number of guests reporting AGE symptoms over the total number of guests at the resort during a given period of time. Resort or "travel package" refers to the cohort of guests staying at the resort over a given period of time. Guests typically arrived and departed on the same days within the package. "Short stay" refers to a travel package lasting between one and five days. “Long stay” refers to a travel package over 5 days.

B. Study Population

The data was taken from the medical surveillance reports of 24 resorts owned by one company and located in various areas within the United States, Mexico, Australia, Caribbean and Europe. The medical records are those of guests and staff reporting symptoms of AGE. Cases of AGE were defined as “three or more episodes of loose stools in a 24 hours period or what is above normal for the individual” or “vomiting and one additional symptom including one or more episodes of loose stools in a 24-hour period, or abdominal cramps, or headache, or muscle aches, or fever (temperature of ≥100.4°F) [25]. The original sample size was 6,088 cases from December 28, 2014 to January 6, 2016. Cases were eliminated if they occurred outside of the year 2015, did not meet the case definition, or had missing data. Resorts were labeled A-X. The two resorts in Australia (Resorts L and N) did not have a full year of guest data so these resorts were eliminated from the analyses. After these exclusions, the sample size for analysis was 4,739 cases of AGE, and 2,475,875 guests and approximately 23,524 staff occupied the 22 resorts in 2015. Exact staff numbers were not given by the resort company so were estimated based on reported staff capacity of each resort.

C. Analytic Approach

The first step was to clean the data and verify that all listed cases met the AGE definition. The data was then sorted by resort location and by the start and end dates of the travel package. At times, fewer than 100 guests would arrive in the midst of a larger travel package, and therefore would have a shorter trip. These guests were included in the cohort arriving earlier for the full trip to simplify attack rate calculations. Leisure packages with no cases were not included in the analysis as specific guest data, such as age and gender, was available only for cases.

The attack rate was calculated as the number of cases over the total number of either guests or staff members for each variable of interest (ex: season, resort). Information on sex and age were included as part of the case data and assumed to be accurate. In order to examine travel duration as a risk factor, travel packages were classified into two groups. The “short stay” included packages from 1-5 days. The “long stay” included packages from 6-15 days. Sizes ranged from very small, small, medium, large and very large resorts. “Very small” resorts included those with a guest capacity ranging from 2,050-2,056, “small” resorts included a capacity of 2,124, “medium” ranged from 2,754-3,002, “large” ranged from 2,980 to 3,012, and “very large” was 3,646-3,690 guests. AGE seasonality was examined by month and season. Month of illness was based on the date the case reported the illness to the health clinic. The seasons were categorized as Spring (March, April, May), Summer (June, July, and August), Fall (September, October November) and Winter (December, January, and February). The time lag between symptom onset and seeking care was calculated by subtracting the date the case sought care from the date the case reported first having symptoms. At times, symptoms would occur before the trip package started, and therefore the time lag would be a negative value. Since it is impossible to calculate an attack rate for these cases, they were excluded from the attack rate analysis. Similarly, the time difference between when the case reported symptoms and the date they arrived at the resort was calculated. This was done to examine the temporal relationship between arrival at the resort and attack rate. Case records included room numbers of the guests and staff, and these were grouped by floor to determine if the distance between the room location (floor) and the resort dining hall used by the guest or staff was related to AGE attack rate. For this analysis, we assumed that distance to dining hall was a proxy for the time spent walking through the resort to reach the dining hall and an opportunity for contact time with public space in the resort. Resorts were labeled A-X, and Resorts L and N were eliminated from the analysis because of incomplete data.

All data were provided by the resort company in an Excel database compiled from medical records. Exported case data included all cases of reported AGE and listed resort arrival date, date and time the case reported symptoms, date and time of symptom onset, room number, dining hall seat, symptoms, guest or staff, and, if applicable, staff position. Total guest occupancy data was compiled using a Hyperion query from Data Warehouse tables and downloaded into Excel. Guest data included start dates of travel packages and room number of guests. Staff data was collected from the company directory of employees at each resort.

In order to test research questions 1, an unpaired t-test was done to compare the difference in attack rates between short and long stays. For the remaining questions, a linear regression was performed with the attack rate for short and long stays as the dependent variable. Individual's status at the resort as guest or staff was included as an independent variable Resort-based factors also included as independent variables were:

time difference between symptom onset and arrival at the resort, time difference between onset of symptoms and seeking care, distance between room floor and dining hall, month, season, size of resort, and resort. Dummy variables were created for categorical values and the reference group was selected based on fewest number of cases because literature suggests using upper or lower boundaries for reference groups [32]. The results of the regression will show how each variable impacts the attack rate, all other known independent variables held equal. Standardized beta values with a p-value less than or equal to 0.05 were considered to be significant.

D. Instruments

The original dataset was received from the company in Microsoft Excel, and all data cleaning was done within Excel. Graphs were also constructed within Microsoft Excel. All analyses were conducted with SAS™ version 9.2.

E. Ethical Considerations

This analysis was determined to be IRB-exempt because it is an analysis of secondary data, and all data were de-identified prior to analysis.

Chapter 3: Results

An AGE outbreak was defined as ≥3.0% of the guests and staff reporting AGE to the resort infirmary [27]. Amongst all 22 resorts, no outbreaks occurred in 2015. The highest attack rate per travel package was 2.76% and the lowest was 0.02%. The case population included men (48%) and women (52%).

Table 1 summarizes the characteristics of the resorts analyzed in the study. Descriptive statistics given for each resort include the size of the resort, length of stay offered by the resort, number of cases in each resort during 2015 as well as total guests and staff at the resort during 2015. Also, the calculated attack rates for short and long stays were included.

Table 1: Characteristics of resorts in 22 resorts, 2015 (N=4,739)

Resort*	Size **	Short Stay, Long Stay, or Both	# of Cases	Total # Guests and Staff in 2015	Attack Rate**** for Short Stay	Attack Rate**** for Long Stay
A	Very small	Both	193	93,271	0.42%	0.18%
B	Very small	Short	172	176,050	0.15%	N/A
C	Very small	Both	140	149,063	0.15%	0.12%
D	Very small	Short	299	105,235	0.64%	N/A
E	Very small	Short	114	88,341	0.20%	N/A
F	Very small	Short	385	105,115	0.25%	N/A
G	Very small	Both	183	98,190	0.61%	0.18%
H	Very small	Short	215	109,648	0.28%	N/A
I	Small	Both	220	108,070	0.20%	0.36%
J	Small	Short	168	144,904	0.18%	N/A
K	Small	Both	219	132,309	0.20%	0.27%
M	Medium	Both	156	74,405	0.17%	0.41%
O	Medium	Long	309	74,846	N/A	0.46%
P	Large	Both	221	106,820	0.11%	0.25%
Q	Large	Both	305	103,824	0.15%	0.43%
R	Large	Both	300	104,663	0.25%	0.46%
S	Large	Both	215	102,777	0.10%	0.45%
T	Large	Both	260	98,932	0.20%	0.44%
U	Large	Both	181	96,610	0.12%	0.24%
V	Very large	Both	241	119,082	0.33%	0.27%
W	Very large	Both	226	126,157	0.09%	0.22%
X	Very large	Long	197	157,563	N/A	0.16%

* Resorts L and N were eliminated from the analysis for having incomplete data
**Size was based on guest capacity: "very small" ranging from 2,050-2,056, "small" resorts: 2,124, "medium" resorts: 2,754-3,002, "large" resorts: 2,980 to 3,012, and "very large" resorts: 3,646-3,690 guests
*** Short stays lasted between 1 and 5 days and long stays lasted 6-15 days
**** Attack rate was calculated as the number of cases over the total number of either guests or staff members for each variable of interest, in this case resort

Table 2 characterized the cases that reported illness in 2015. Descriptive statistics in this table include the number of cases for each variable, such as the month, the percent of cases for the variable compared to other cases, and means and standard deviations where applicable.

Table 2. Characteristics of cases in 22 resorts, 2015 (N=4,739)

	# of Cases	%	Mean	Standard Deviation
Gender				
Male	2275	48	--	--
Female	2464	52	--	--
Age				
0-14 years	350	6.79		
15-24 years	727	14.10	41.2	19.4
25-54 years	2,637	51.14		
55-64 years	643	12.47		
65+ years	799	15.49		
Guest/Staff				
Guest	3,647	77	--	--
Staff	1,092	23	--	--
Month				
January	328	6.92	--	--
February	456	9.62	--	--
March	473	9.98	--	--
April	433	9.14	--	--
May	449	9.47	--	--
June	426	8.99	--	--
July	441	9.31	--	--
August	356	7.51	--	--
September	331	6.98	--	--
October	315	6.65	--	--
November	348	7.34	--	--
December	363	7.66	--	--
Season				
Spring	1356	28.61	--	--
Summer	1223	25.81	--	--
Fall	994	20.97	--	--
Winter	1147	24.20	--	--

Days between Onset of Symptoms and Start of Travel Package (Days)	--	--	1.88	2.00
Days between Onset of Symptoms and Reporting of Symptoms (Days)	--	--	0.52	0.87
Distance from Room to Dining Hall (Floors)*	--	--	2.60	2.11

*Distance defined as number of floors between guest and staff room and dining hall

Tables 3 and 4 produced the results from the linear regression conducted for both short and long stays. Significant p-values ($p \leq 0.05$) are bolded.

Table 3. Linear regression coefficients modeling short stay attack rates as a function of AGE risk factors in 22 resorts, 2015

Table 3 (Cont.)

Parameter Estimates (Short Stays)			
Variable	Beta	Standard Error	P-value*
Intercept	0.00108	0.00070	0.1271
Guest or Staff			
Guest	0.00109	0.00032	**0.0006**
Staff	Ref		
Resort			
A	0.00185	0.00050	**0.0002**
B	-0.00027	0.00050	0.5923
C	-0.00086	0.00052	0.0966
D	0.00358	0.00045	**<0.0001**
E	Ref		
F	0.00064	0.00048	0.1815
G	0.00336	0.00049	**<0.0001**
H	0.00100	0.00047	**0.0361**
I	-0.00010	0.00085	0.9034
J	-0.00003	0.00049	0.9553
K	-0.00018	0.00049	0.7164
M	0.00073	0.00236	0.7587
O	N/A	.	.
P	-0.00179	0.00103	0.083
Q	0.00061	0.00115	0.5971
R	-0.00002	0.00091	0.9845
S	-0.00083	0.00122	0.4977
T	-0.00083	0.00115	0.4693
U	-0.00068	0.00150	0.652
V	0.00063	0.00101	0.5331
W	-0.00224	0.00126	0.0763
X	N/A	.	.
Size			
Very small	0.00048	0.00259	0.8526
Small	-0.00142	0.00260	0.585
Medium	-0.00182	0.00263	0.4888
Large	Ref		
Very large	-0.00126	0.00272	0.6428

Parameter Estimates (Short Stays)			
Variable	Beta	Standard Error	P-value*
Month			
January	0.00033	0.00047	0.4813
February	0.00147	0.00044	**0.001**
March	0.00008	0.00044	0.853
April	-0.00012	0.00044	0.7916
May	0.00418	0.00043	**<0.0001**
June	0.00253	0.00045	**<0.0001**
July	-0.00063	0.00045	0.1628
August	-0.00028	0.00045	0.5348
September	-0.00010	0.00046	0.8211
October	Ref		
November	-0.00061	0.00050	0.2172
December	-0.00034	0.00044	0.4336
Season		.	.
Fall	Ref	.	.
Winter	0.00068	0.00030	**0.0238**
Spring	0.00177	0.00029	**<0.0001**
Summer	0.00064	0.00030	**0.0318**
Days between Onset of Symptoms and Start of Travel Package	0.00004	0.00007	0.5426
Days between Onset of Symptoms and Reporting	-0.00037	0.00013	**0.0043**
Distance between Floor of Room and Dining Hall**	0.00015	0.00008	0.0487

*P-value significant when $p \leq 0.05$

**Distance defined as number of floors between guest and staff room and dining hall

Table 4. Linear regression coefficients modeling long stay attack rates as a function of AGE risk factors in 22 resorts, 2015

Parameter Estimates (Long Stays)			
Variable	Beta	Standard Error	P-value*
Intercept	-0.00451	0.00324	0.1634
Guest or Staff			
Guest	0.00149	0.00020	**<0.0001**
Staff	Ref		
Resort			
A	0.00298	0.00327	0.3625
B	N/A		
C	Ref		
D	N/A		
E	N/A		
F	N/A		
G	0.00255	0.00452	0.573
H	N/A		
I	0.00479	0.00321	0.1353
J	N/A		
K	0.00367	0.00325	0.259
M	0.00543	0.00321	0.0907
O	0.00591	0.00320	0.0653
P	0.00395	0.00321	0.2186
Q	0.00565	0.00321	0.0783
R	0.00592	0.00321	0.0647
S	0.00591	0.00321	0.0656
T	0.00567	0.00321	0.0772
U	0.00374	0.00321	0.2441
V	0.00399	0.00321	0.2141
W	0.00408	0.00321	0.2037
X	0.00298	0.00321	0.3524
Size			
Very small	-0.00252	0.00069	**0.0003**
Small	-0.00095	0.00027	**0.0005**
Medium	-0.00038	0.00018	**0.0334**
Large	Ref		
Very large	-0.00203	0.00021	**<0.0001**

Table 4 (Cont.)

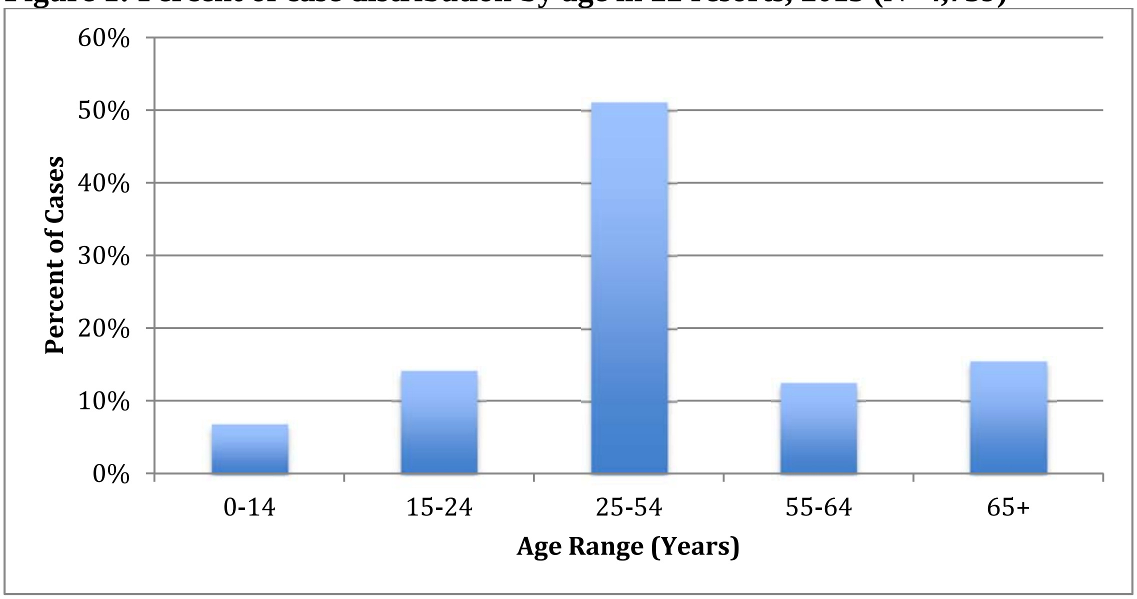
Parameter Estimates (Long Stays)			
Variable	Beta	Standard Error	P-value*
Month			
January	0.00199	0.00035	**<0.0001**
February	0.00289	0.00033	**<0.0001**
March	0.00200	0.00033	**<0.0001**
April	0.00107	0.00033	**0.0014**
May	0.00086	0.00034	**0.0109**
June	0.00239	0.00033	**<0.0001**
July	0.00212	0.00033	**<0.0001**
August	0.00078	0.00035	**0.0276**
September	0.00095	0.00035	**0.0074**
October	Ref		
November	0.00177	0.00034	**<0.0001**
December	0.00028	0.00035	0.4268
Season		.	.
Fall	Ref	.	.
Winter	0.00019	0.00019	**<0.0001**
Spring	0.00024	0.00018	0.7234
Summer	0.00083	0.00019	**<0.0001**
Days between Onset of Symptoms and Start of Travel Package	0.00014	0.00003	**<0.0001**
Days between Onset of Symptoms and Reporting	-0.00021	0.00007	**0.0023**
Distance** between Floor of Room and Dining Hall	-0.00003	0.00003	0.2996

*P-value significant when p≤ 0.05

**Distance defined as number of floors between guest and staff room and dining hall

Since overall age data for the resort population was not available, only the distribution of cases across age groups could be examined. Ages of cases ranged from 0 to 95 with the average age being 41 (median=38 and mode=25). Figure 1 shows the distribution of AGE cases by age for all the resort locations in 2015. The highest percent of cases (51%) were among the 25-54 year age group and the lowest proportion of cases were in children under 15 years (6.8%).

Figure 1: Percent of case distribution by age in 22 resorts, 2015 (N=4,739)



The first research question examined the difference in attack rates between guests and staff. Overall, almost 77% of the AGE cases were among guests (Fig 2). There was a significant difference between the attack rates among guests and staff for both short and long stays (Figs 3 and 4). The attack rate for short stays was almost 0.37% for guests and almost 0.18% for staff. For long stays, it was about 0.41% for guests and 0.23% for staff. There was a significant and positive association between guests and attack rates (staff used as reference group). These findings suggest that guests were more likely than staff to develop AGE, all other known variables held equal.

Figure 2: Distribution of AGE cases by guests and staff in 22 resorts, 2015 (N=4,739)

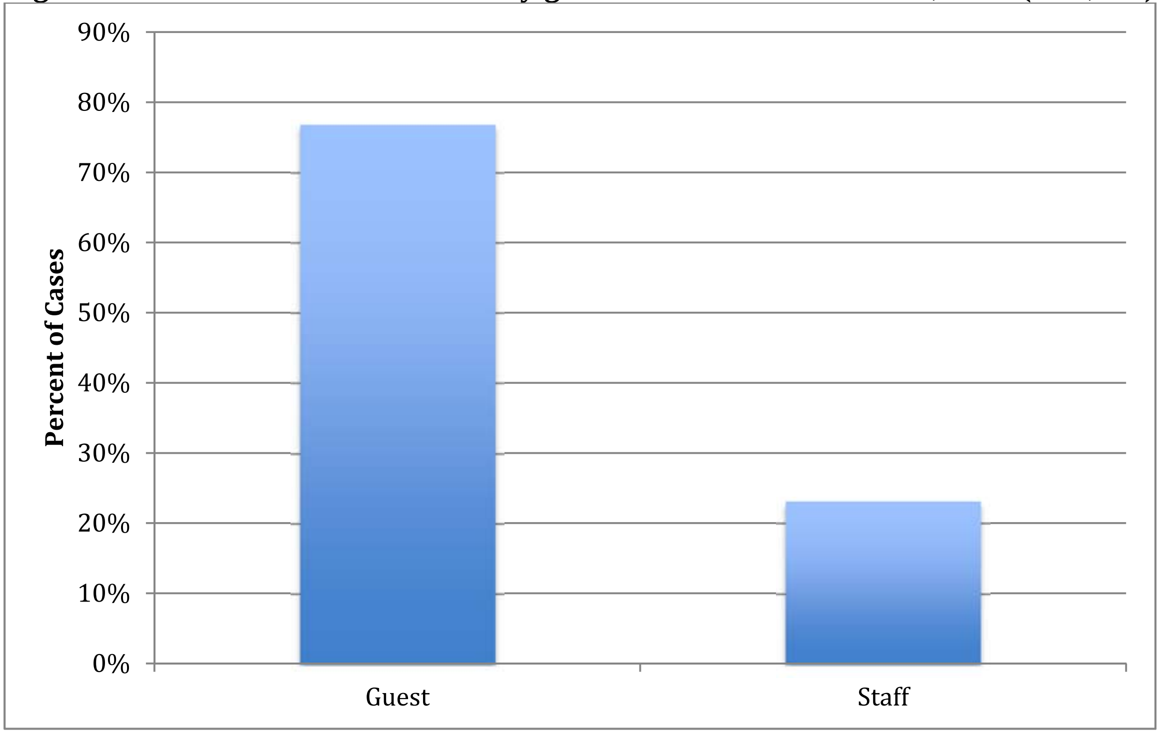


Figure 3: AGE attack rates for guests and staff on short travel packages in 22 resorts, 2015

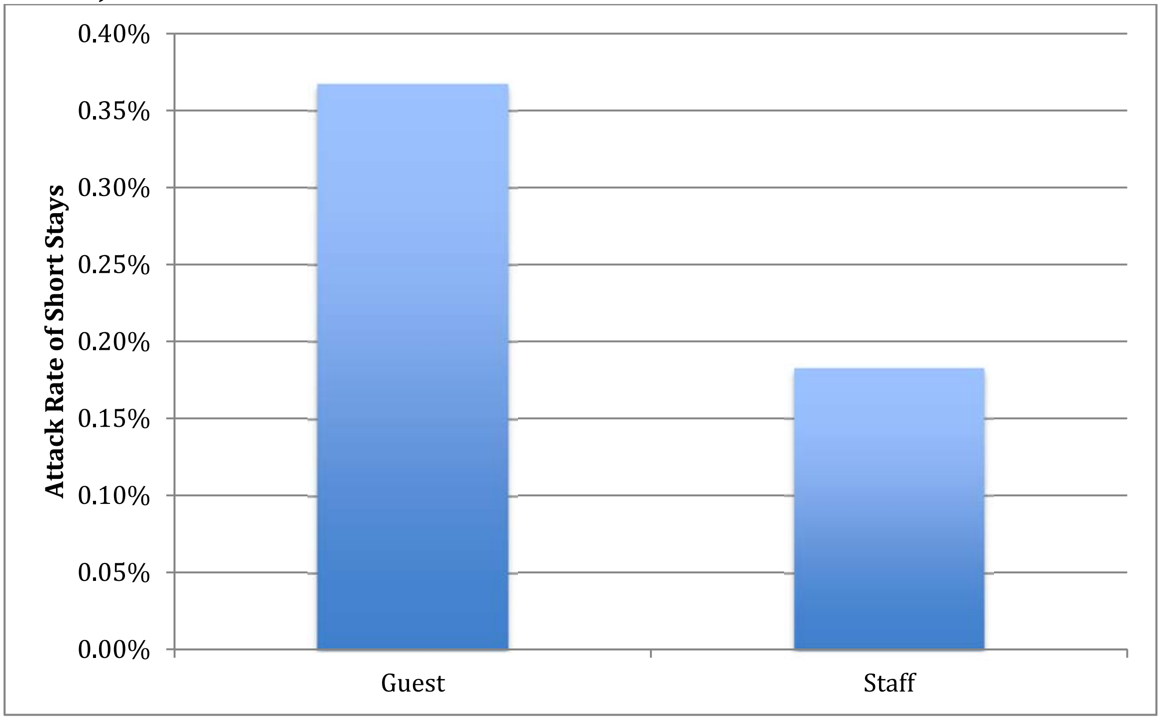
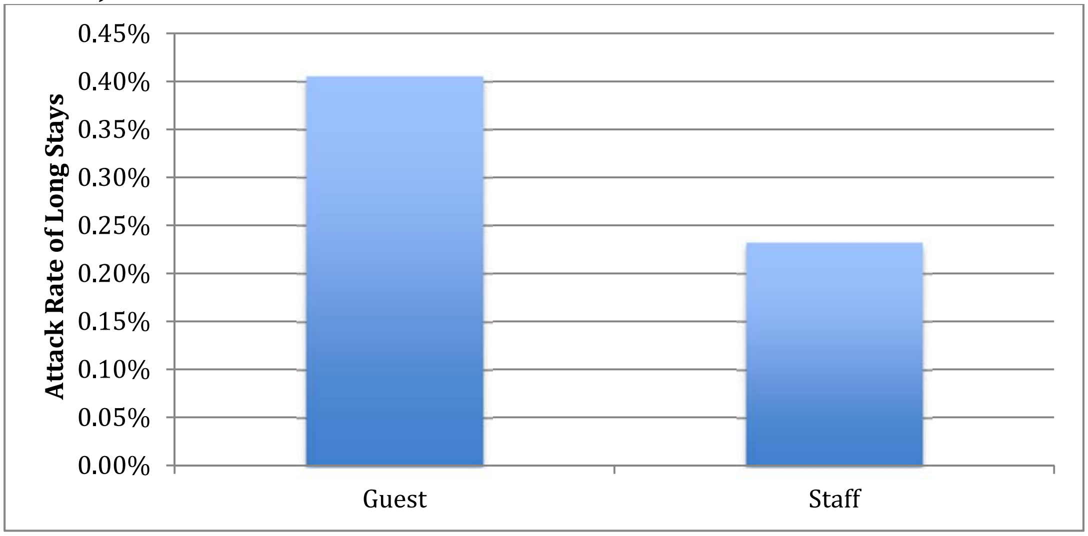


Figure 4: AGE attack rates for guests and staff on long travel packages in 22 resorts, 2015



We studied specific resorts to see if there was a difference in attack rates. Figure 5 shows the distribution of cases by resort. Resort F had the highest proportion of cases (8.12%) and this was almost 2% higher than the resort with the second highest proportion of cases (Resort O). Resort E had the lowest proportion of cases (2.41%). When examining attack rates by resort, Resorts D and G had the highest attack rates (0.64% and 0.61%) and Resort W had the lowest rate (0.09%) for short travel packages (Figure 6). For long travel packages, there was less variance in the attack rates. Resort R had the highest attack rate (0.46%) and Resort C had the lowest (0.01%) for long travel packages (Figure 7). Results for the resort variable from the linear regression for short stays found positive associations between attack rates and cases from resorts A, D, G, and H using E as the reference group. In other words, these resorts had significantly higher attack rates than those from resort E. The regression results from long stays did not show any significant association between a resort and their attack rate. Resort C was used as the reference group for long stays as E did not have any cases for long stays.

Figure 5: Distribution of cases by resort, 22 resorts, 2015 (N=4,739)

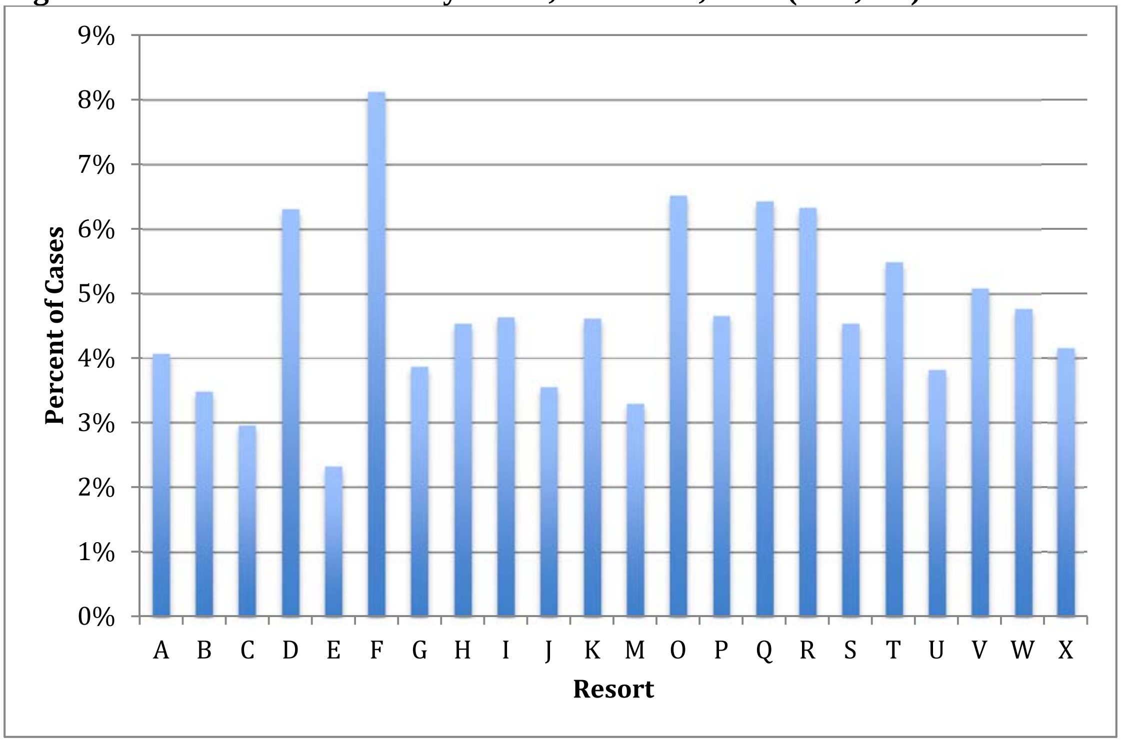


Figure 6: AGE attack rates by resort for short travel packages in 22 resorts, 2015

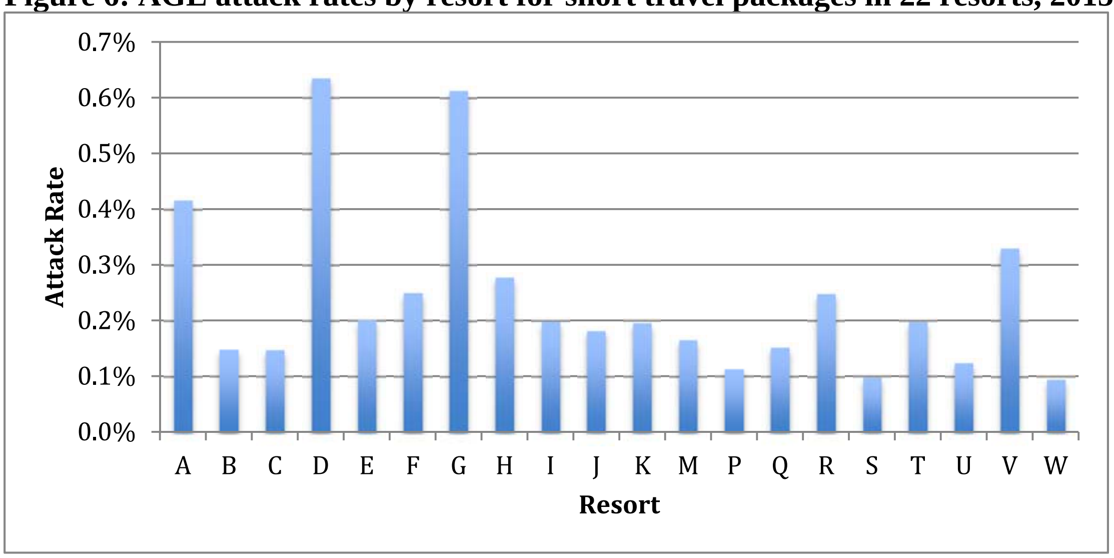
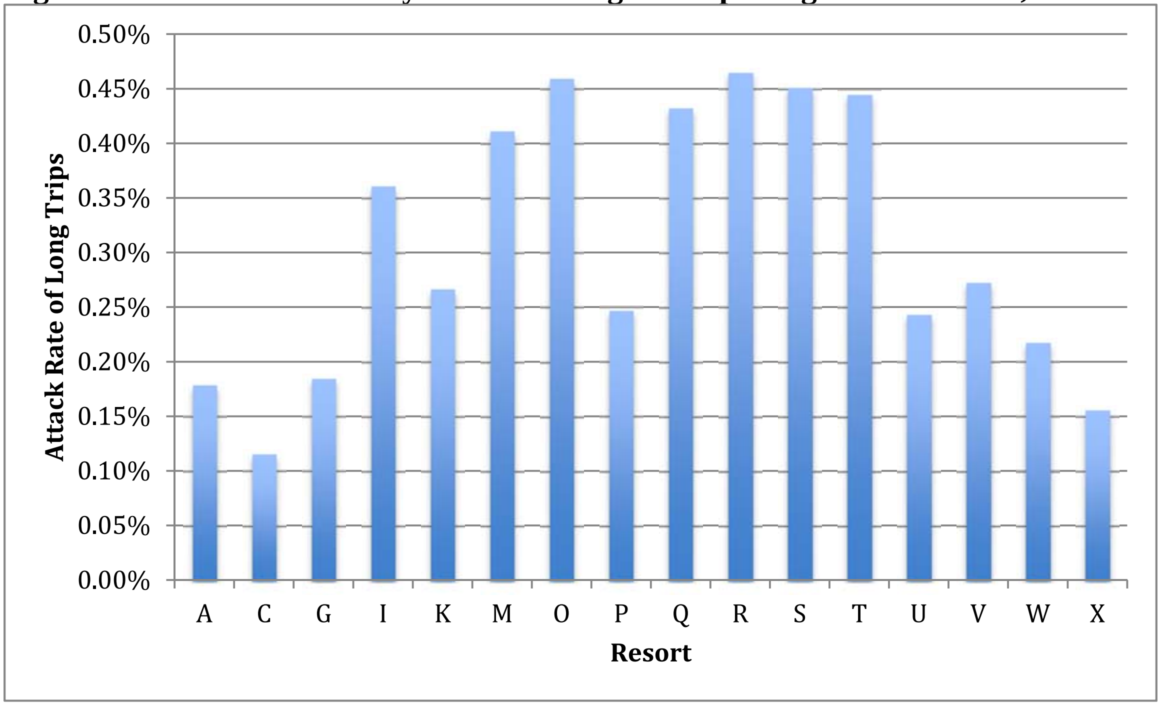


Figure 7: AGE attack rates by resort for long travel packages in 22 resorts, 2015



We also examined the effect of resort size on AGE attack rate. Sizes ranged from very small (8 resorts), small (3 resorts), medium (2 resorts), large (6 resorts), and very large (3 resorts) depending on guest capacity. Figure 8 shows the distribution of cases by resort size. Very small and medium sized resorts were found to have a higher number of cases than the rest, exceeding them by at least 20%. When looking at attack rates by size (Figs 9 and 10), short stay packages had the highest rate amongst the smallest sized resort ("Very small", 0.37%) and the lowest amongst "medium" resorts (0.17%). For long stays (Fig 27), the "very small" resorts also had the smallest attack rate and the highest was found in the large resort (18% and 50%). For short stays, no ship sizes had any significant association with attack rates. For long stays, "very small", "small", "medium", and "very large" resorts all had significantly positive association with attack rates. Large resorts were used as the reference group. The association shows that compared to the large resorts, guests and staff at all other sized resorts were less likely to become cases.

Figure 8: Distribution of cases by resort size, 22 resorts, 2015 (N=4,739)

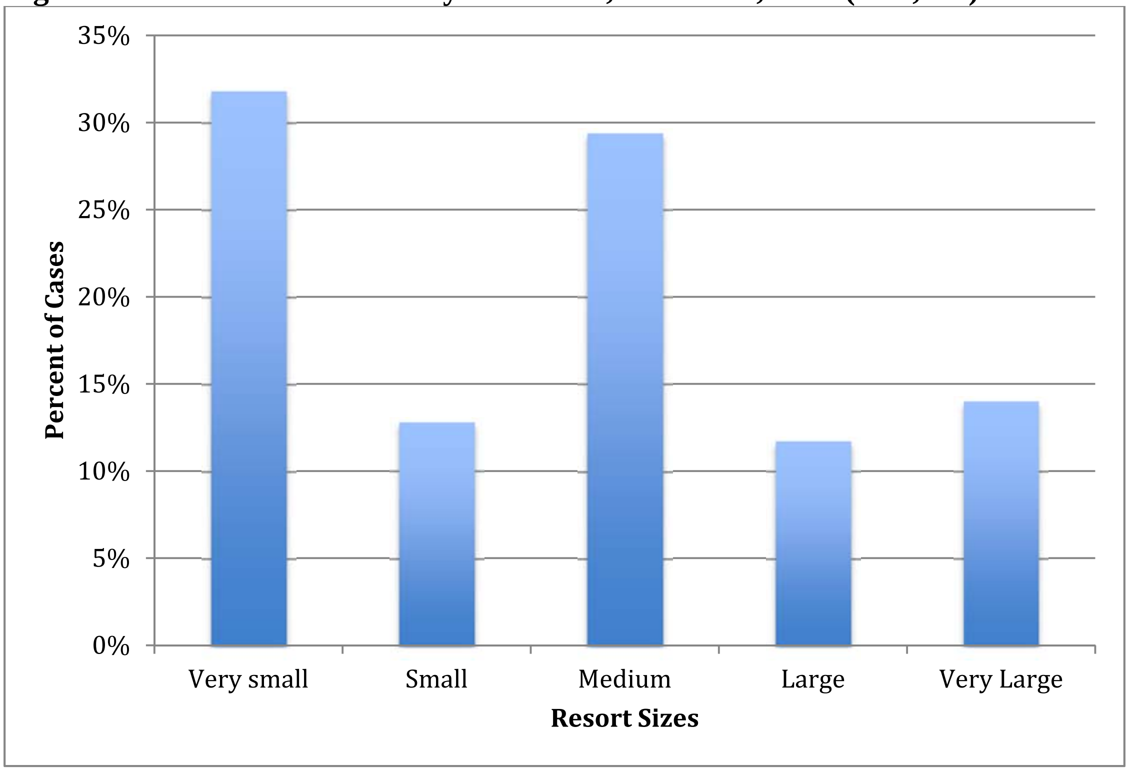


Figure 9: AGE attack rate for short stays by resort size, 22 resorts, 2015

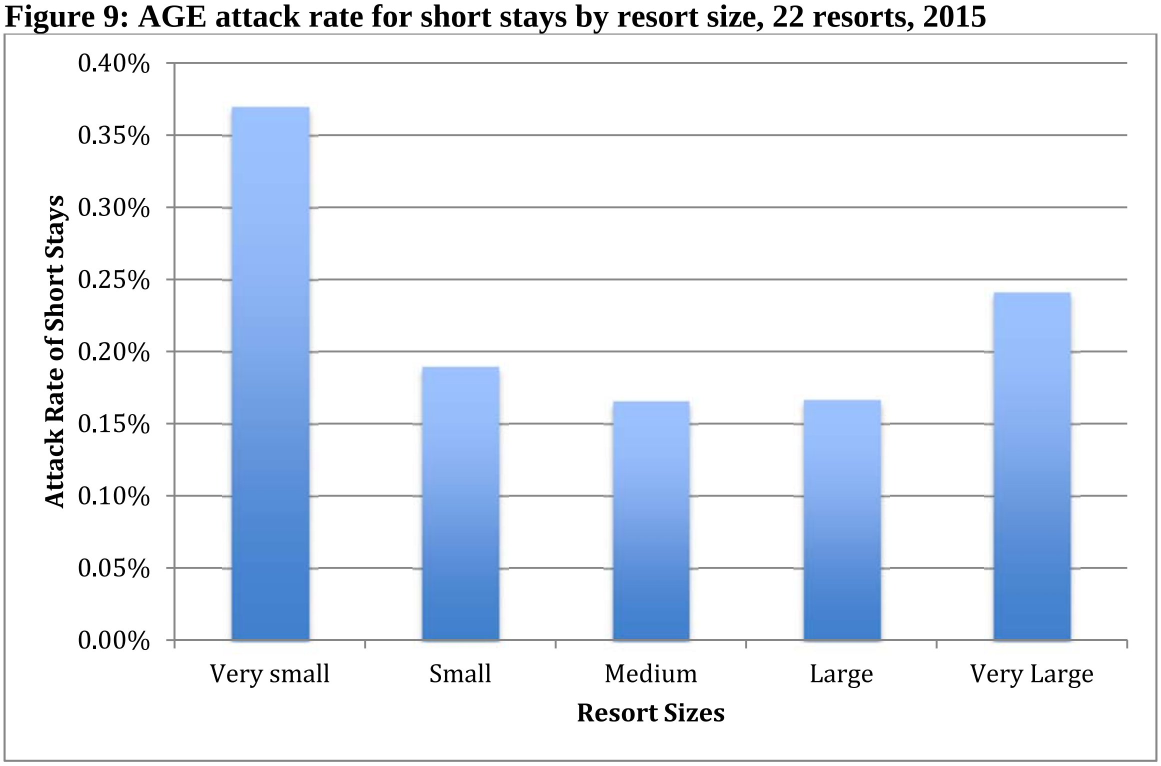
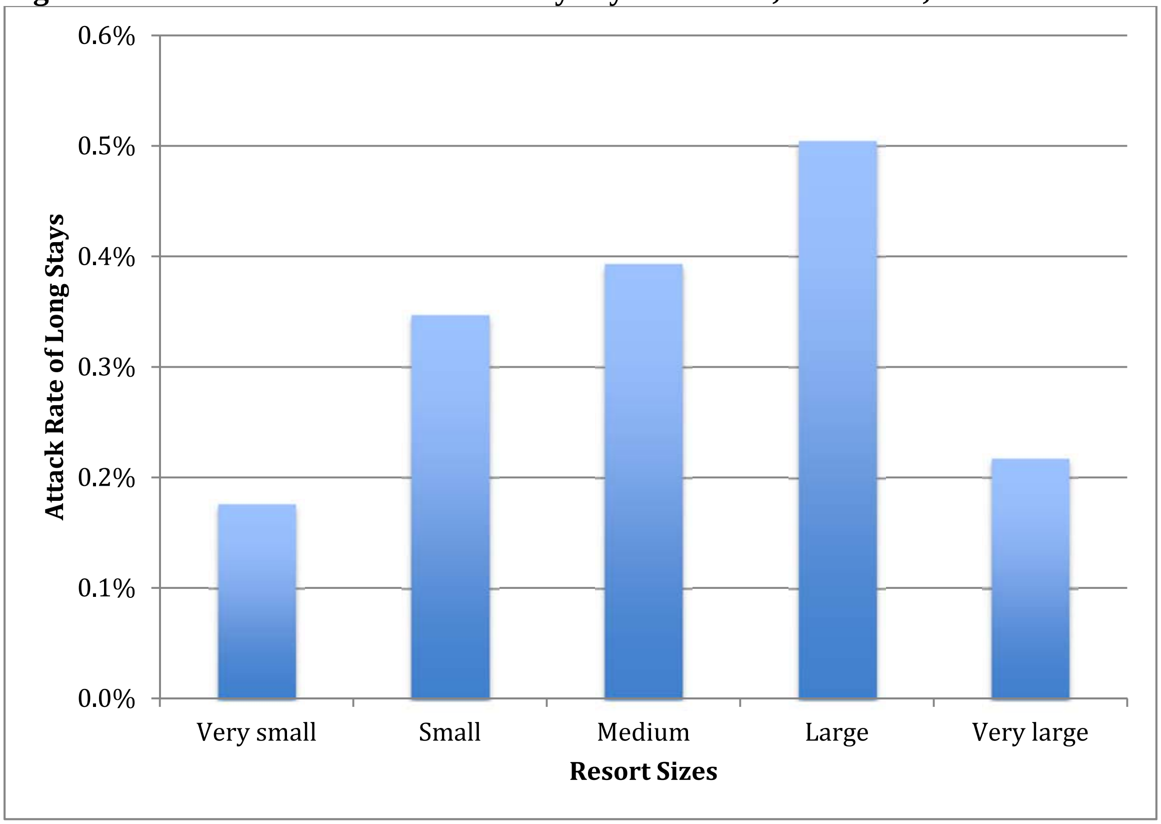


Figure 10: AGE attack rate for short stays by resort size, 22 resorts, 2015



We also examined temporal differences in AGE cases and attack rates by month and season. Figures 11 and 12 show the distribution of cases for each resort by month and season. Although the highest proportion of cases were in March and the spring months, there was little variation across the months. Because there is temporal variation in the number of travelers, we also compared AGE attack rates by month and season (Figures 13-16). For example, although March the highest number of cases, the attack rates for short and long stays were lower because there were more total guests during this month. For short stays, May had the highest attack rate and August had the lowest (0.74% and 0.18%, respectively). Spring still had the highest attack rate for short stays and fall had the lowest rate (0.43% and 0.23%). For long stays, February had the highest attack rates, and summer was the highest season (0.49% and 0.40%, respectively). The lowest attack rates were in October and the fall (0.21% and 0.30%). Full regression results can be found in tables 4 and 5 for short and long stays, but February, May, and summer and winter all had significantly higher attack rates compared to the reference categories.

Figure 11: Distribution of AGE cases by month in 22 resorts, 2015 (N=4,739)

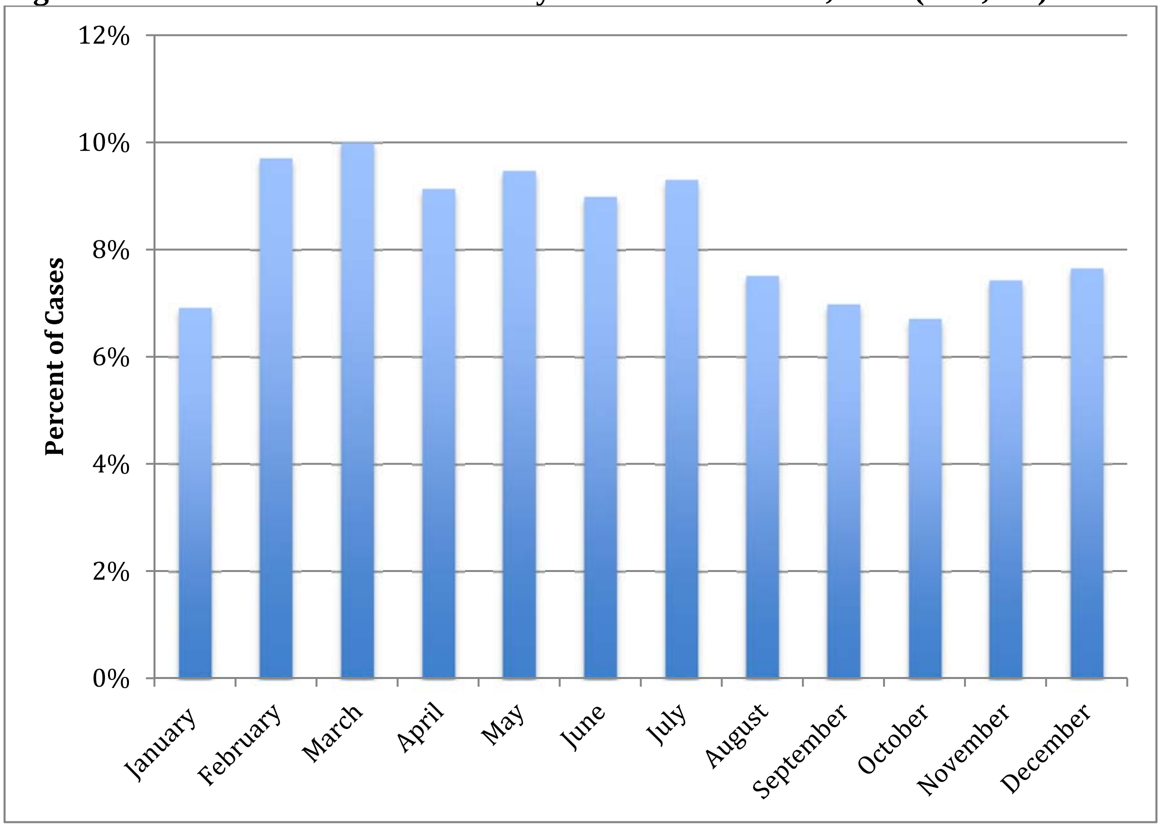


Figure 12: Distribution of AGE cases by season in 22 resorts, 2015 (N=4,739)

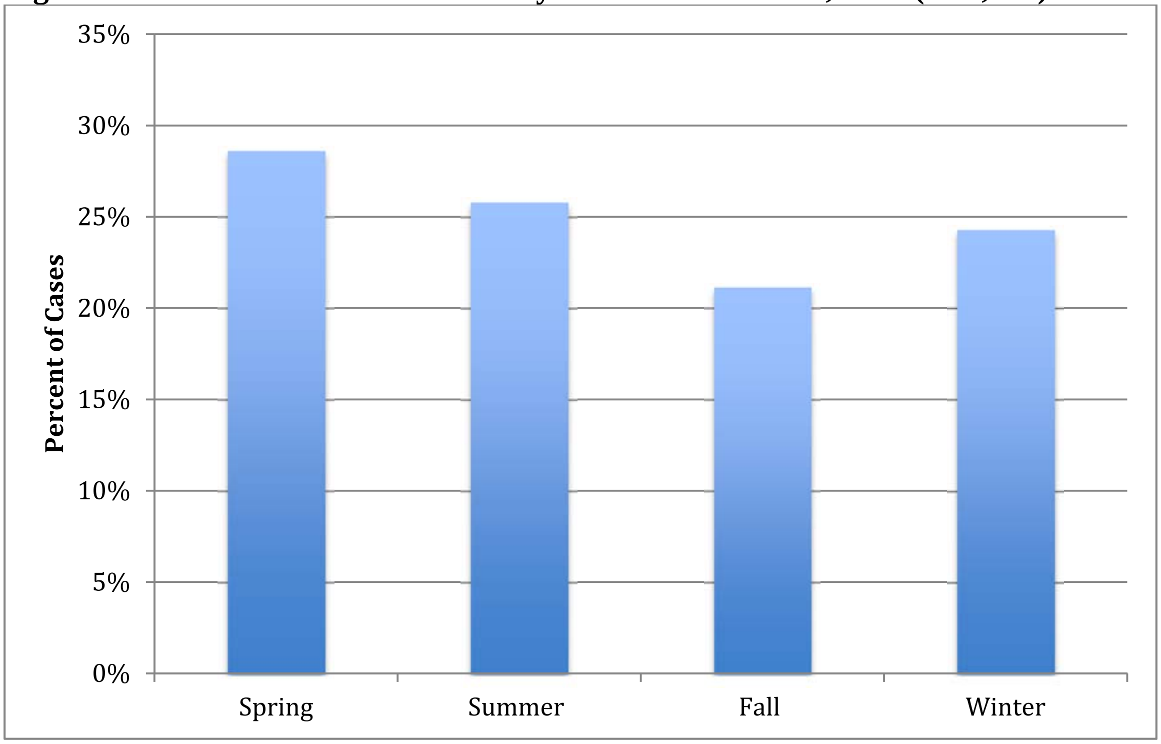


Figure 13: AGE attack rates on short stays by month in 22 resorts, 2015

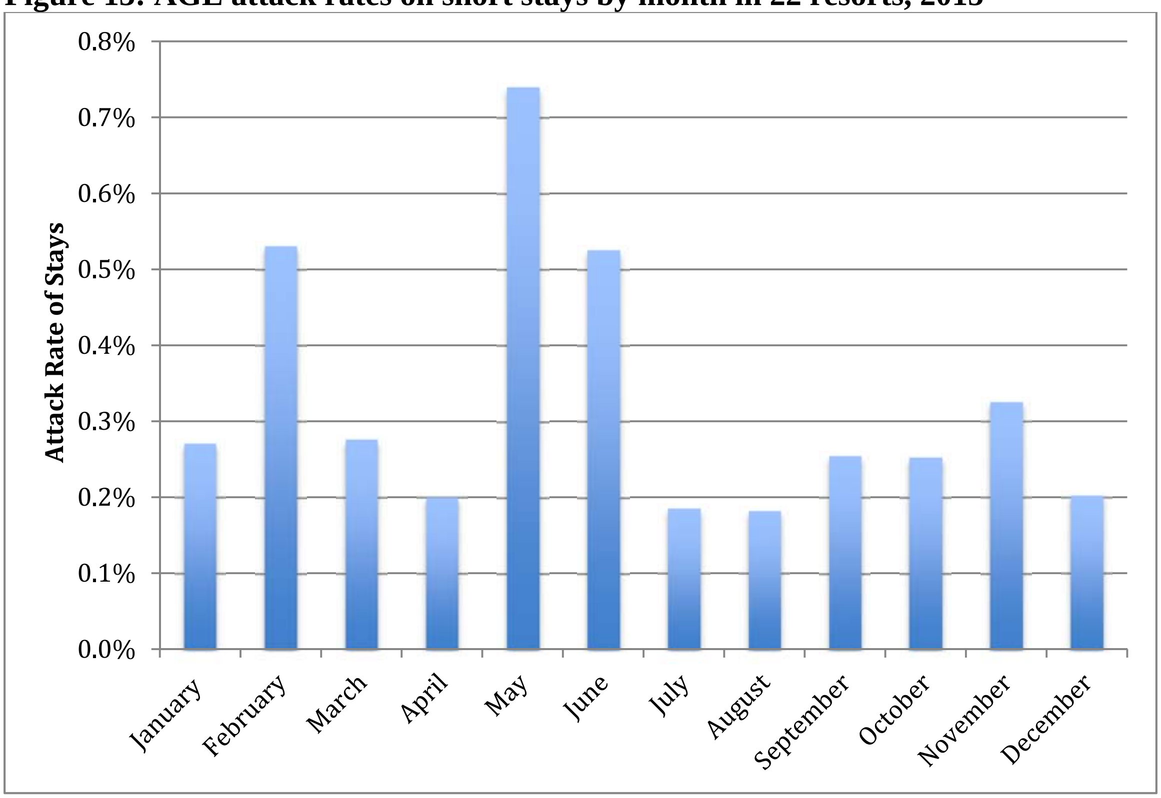
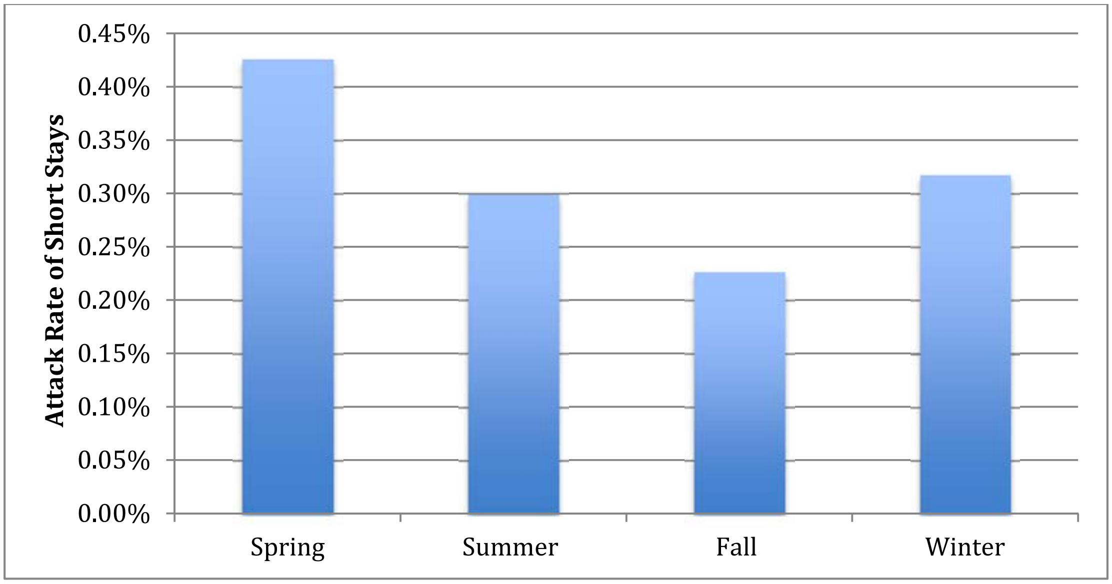


Figure 14: AGE attack rates on short stays by season in 22 resorts, 2015



Figures 15: AGE attack rates on long stays by month in 22 resorts, 2015

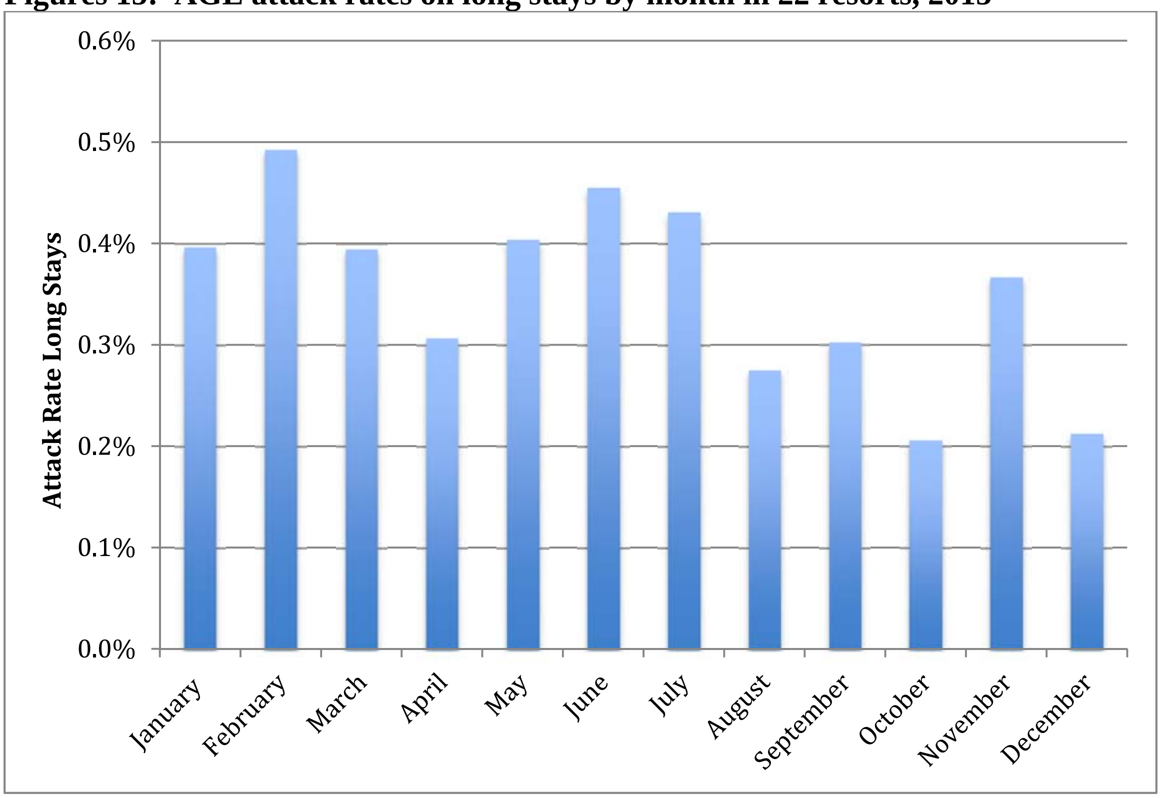
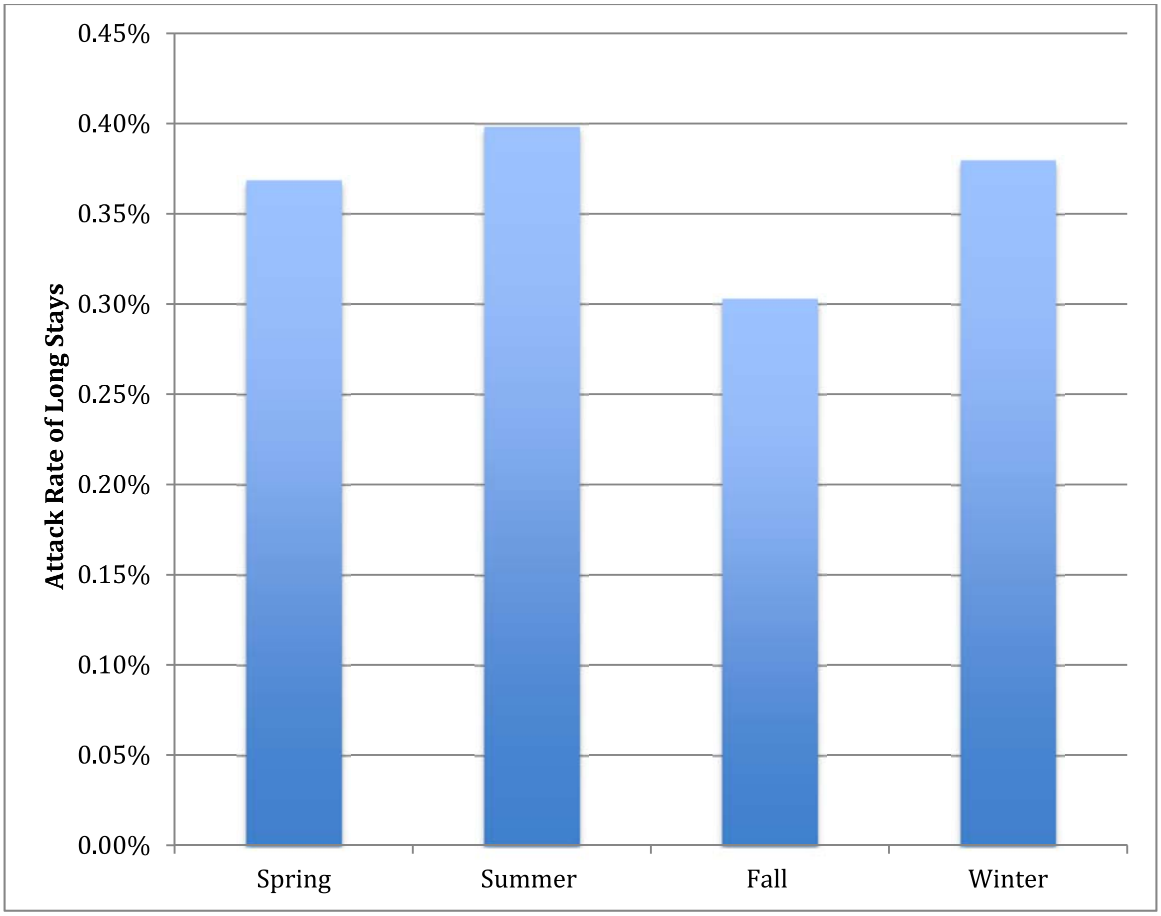


Figure 16: AGE attack rates on long stays by season in 22 resorts, 2015



We also studied the effect of the length of the stay on the attack rate. The length of stay at the resort ranged from 1 to 15 days. The most common trip length was 7 days. The travel packages were classified by short (1-5 days) and long stays (6-15 days), and 2,749 of the cases (58%) occurred during short stays, and the remaining 1,990 cases (42%) occurred during long stays. Short stays had a significantly higher attack rate (0.36%) compared to the long stays (0.32%). The p-value from the unpaired t-test was 0.0039, suggesting a significant difference between short and long stays.

We also examined the timing of a case relative to the start of the travel package to determine if there was an effect on the AGE attack rate. Figure 20 shows the distribution of cases by the day of symptom onset relative to the start of the travel package. The overall distribution of symptom on set ranged from 5 days before the start of the trip to 14 days after the start of the trip with an average of 2.85 days (median=3 days). The majority of cases started within 0-6 days after arrival, with most cases experiencing an onset of symptoms on the third day of the trip (16.5%). A small percentage, 0.17%, of the cases started before the guests arrived at the resort. Since negative cases were excluded from attack rate calculations, the range for short stays was between 0 and 4 days with an average of 1.88 days (median and mode=2 days). Figure 21 shows that the highest attack rate for short stays was for those experiencing symptoms four days after the start of travel package (0.44%) and the lowest attack rate was for one day (0.21%). For long stays, the range was 0 to 14 with an average of 3.55 days, as shown in Figure 22 (median=4 days and mode=5 days). The highest attack rate for long stays was for those experiencing symptoms nine days after the start of travel package (0.47%) and the lowest attack rate was for fourteen days (0.18%). For long stays, a significant, positive association was found between the start of the travel package and the onset of symptoms.

Figure 17: Distribution of cases by day of symptom onset relative to the start of the travel package (Day 0) in 22 resorts, 2015 (N=4,739)

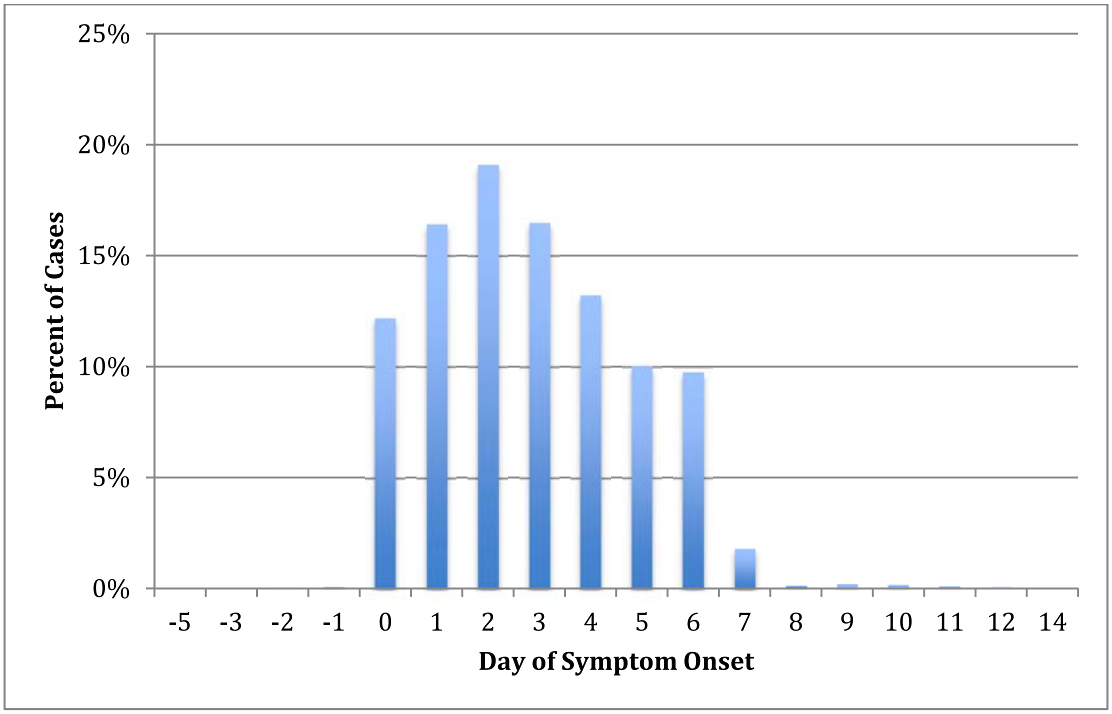


Figure 18: AGE attack rates for short stays by day of symptom onset in 22 resorts, 2015

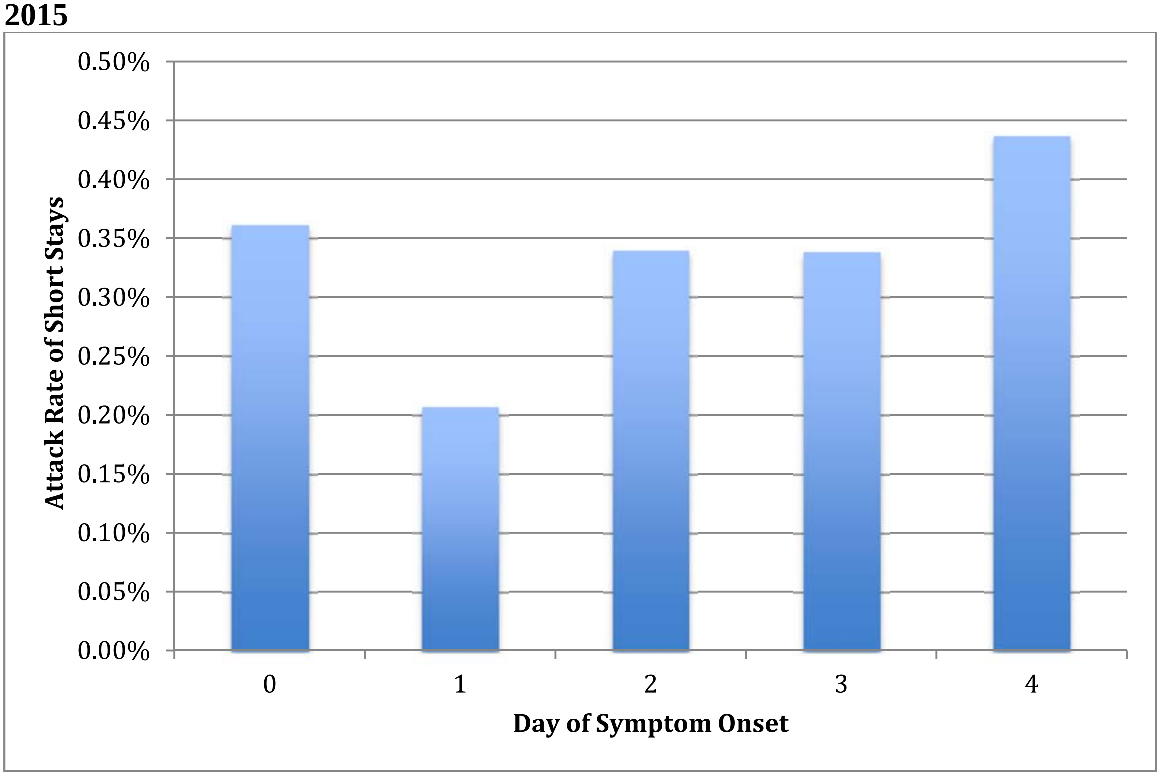
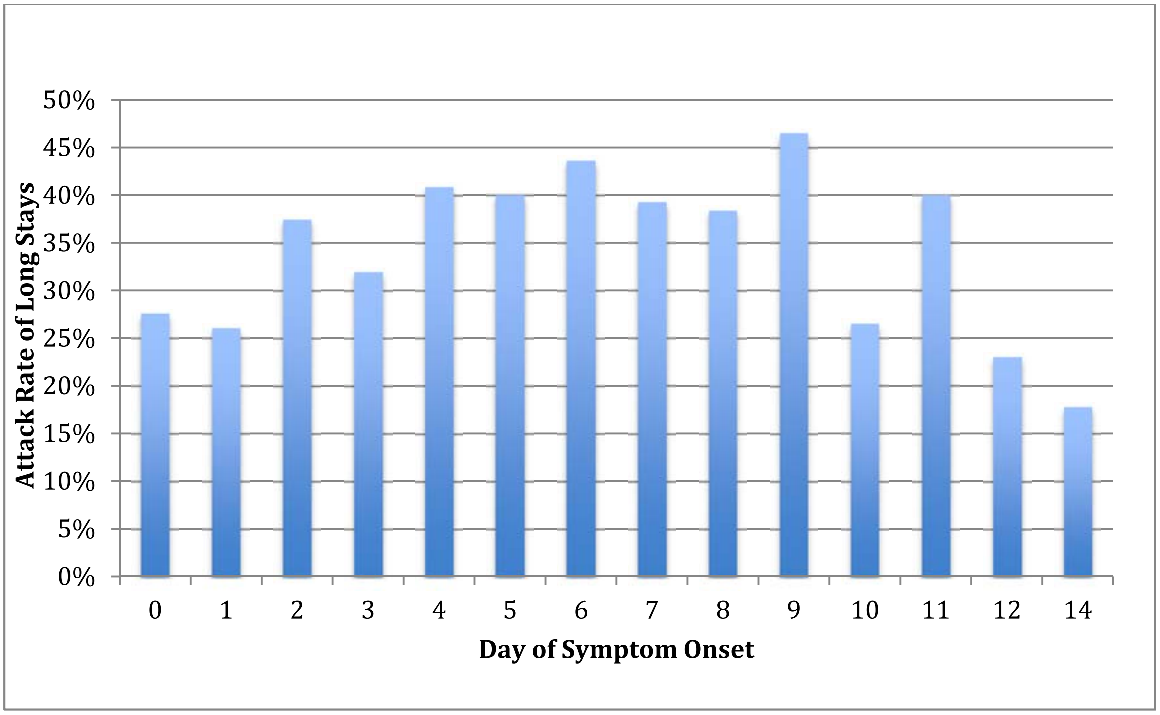


Figure 19: AGE attack rates for long stays by day of symptom onset in 22 resorts, 2015



We also studied the impact of a delay in case reporting on the attack rate for each cohort of guests. The average time it took for a case to report to the resort's medical office after symptoms occurred was 0.52 days (median and mode=0 days). Figure 20 shows the distribution of cases by the day of case reporting relative to symptom onset. Over 60% of cases visited the medical office on the day AGE symptoms started. However, some guests waited until as long as 16 days after symptom onset before reporting to the medical office. Again, cases experiencing symptoms before arriving at the resort were included in case distribution, but not in attack rates. Figures 21 and 22 show the attack rates by day of case reporting relative to symptom onset. For both short and long stays, a delay in case reporting of 6 days was associated with the highest attack rates. A six day delay in case reporting was associated with a much higher attack rate for long stays, and was about 0.18% higher than the second highest attack rate (0.58% versus 0.40%). For both short and long stays, a small, but significant, negative association was observed between the attack rate and time difference between onset of symptoms and case reporting.

Figure 20: Distribution of cases by the day of case reporting relative to symptom onset in 22 resorts, 2015 (N=4,739)

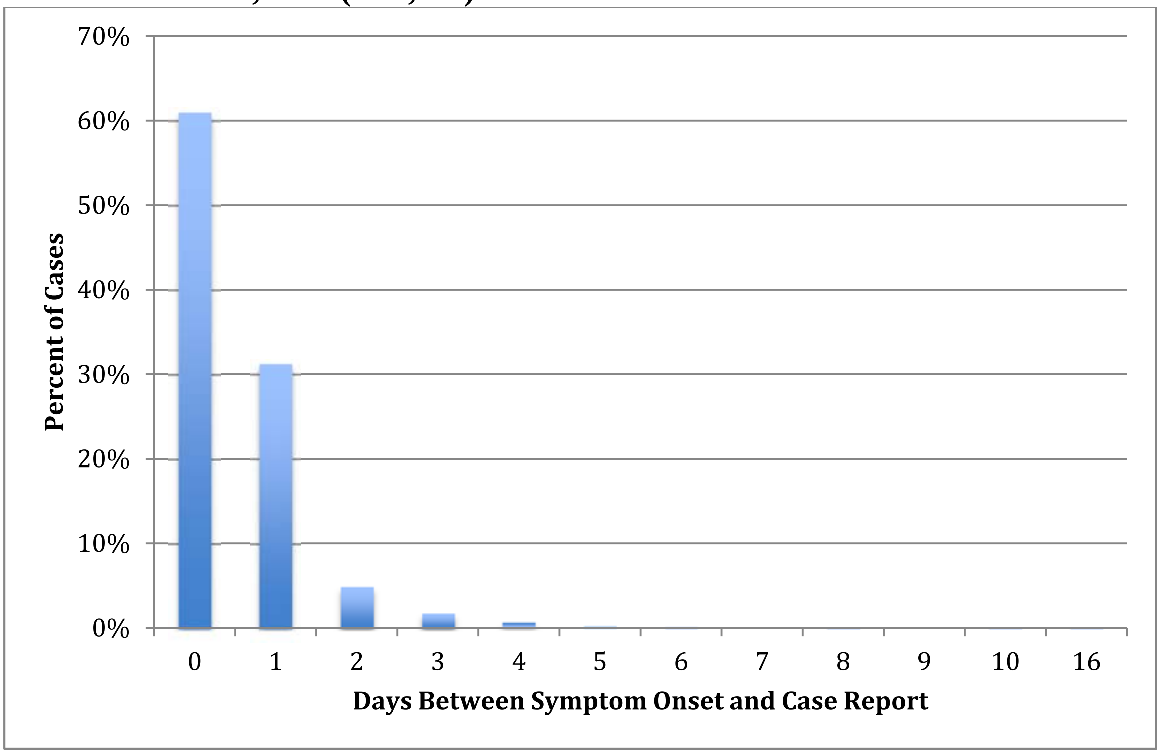


Figure 21: AGE attack rate for short stays by the day of case reporting relative to symptom onset in 22 resorts, 2015

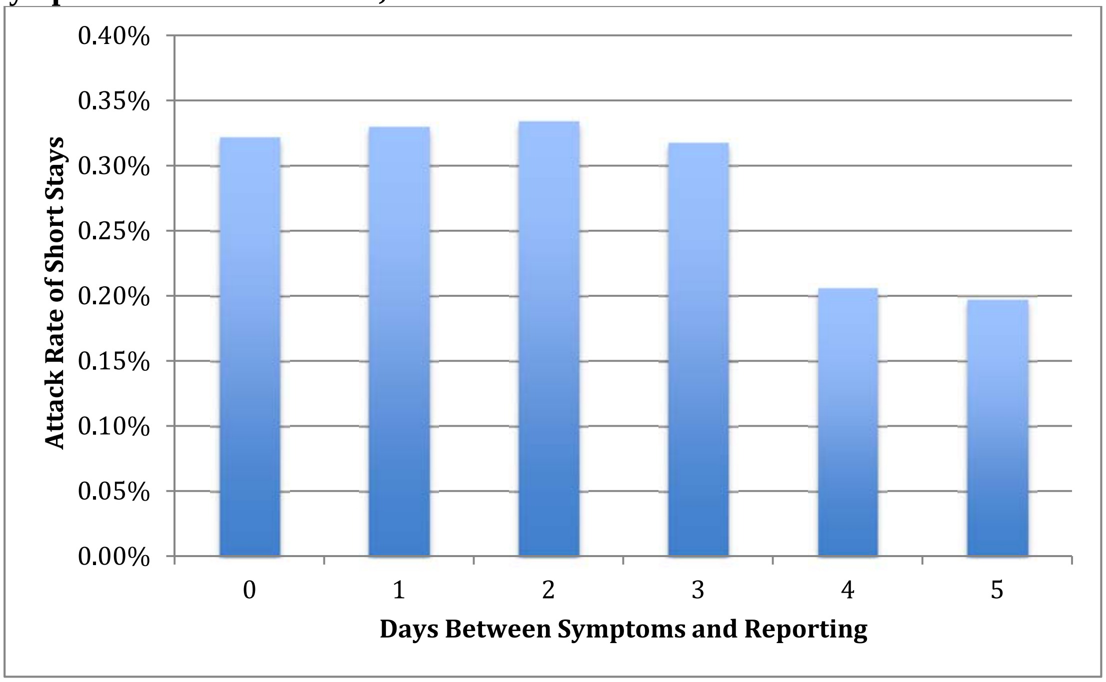
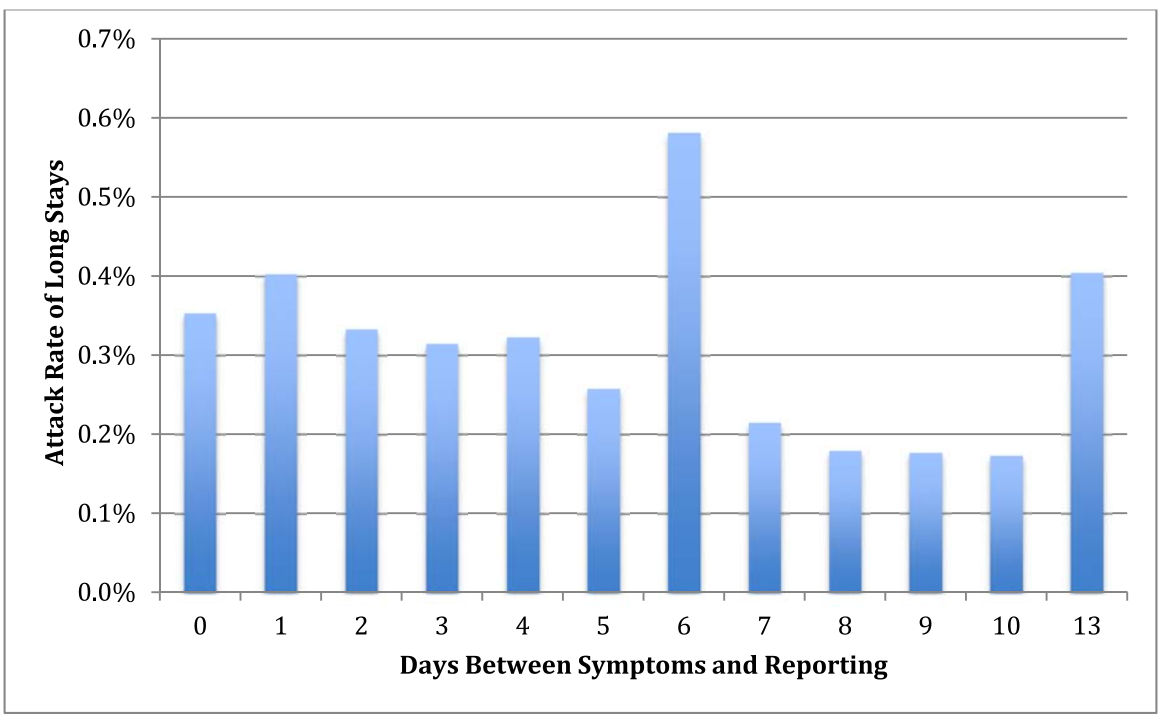


Figure 22: AGE attack rate for long stays by the day of case reporting relative to symptom onset in 22 resorts, 2015



We then examined the effect of spatial distance between a guest or staff room at the resort (using floor of the resort as a proxy) and the dining hall on the AGE attack rate. Figure 23 shows the distribution of cases by distance to the dining hall based on the number of floors between the two locations. The average distance between the resort room and the dining hall of cases was 2.60 floors (median=2 floors and mode=1 floors). Staff members almost always lived on the same floor as their dining area. Figures 24 and 25 show that on short stays the attack rates were highest among those who had rooms that were 4-6 floors away from the dining hall (0.49% for both short and long stays). The lowest attack rate was for guests and staff who had rooms that were 12 floors away from the dining hall on both short and long stays (0.11% and 0.12%). Short stays generally had higher attack rates among those living father from the dining hall, while longer trips had higher attack rates among those living closer to the dining hall. There was no significant association between attack rate and distance to dining hall for either short or long stays.

Figure 23: Distribution of AGE cases by the distance between the residence room and the dining hall in 22 resorts, 2015 (N=4,739)

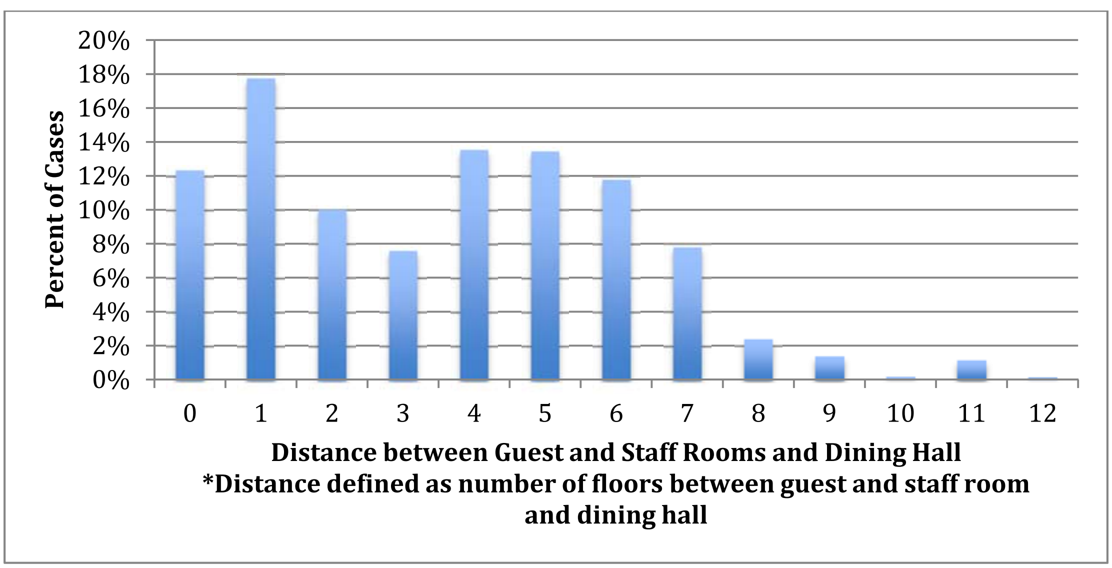
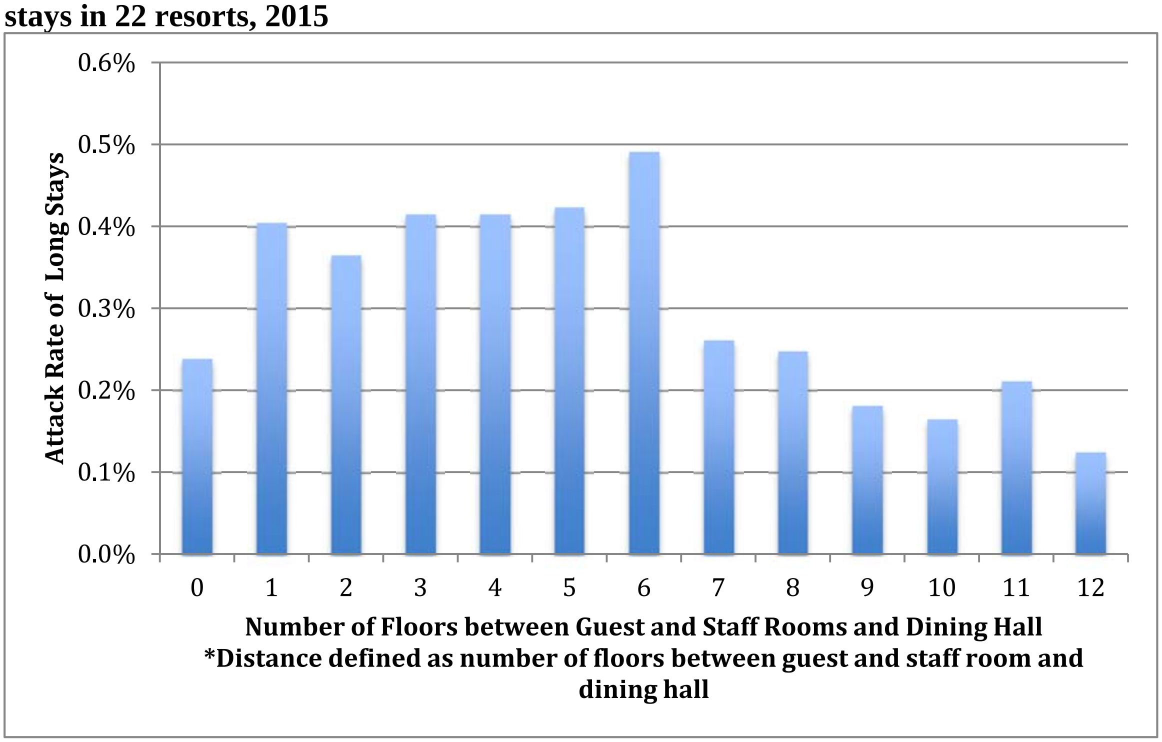


Figure 24: AGE attack rates by distance from residence room to dining hall for short stays in 22 resorts, 2015

Figure 25: AGE attack rates by distance from residence room to dining hall for long stays in 22 resorts, 2015



Chapter 4: Discussion

A: Summary of the Findings

The goal of this analysis was to characterize epidemiologic patterns and risk factors for AGE in leisure settings. Detailed case and occupancy data was included from 22 resort settings over a whole year (2015), and this unique data set allowed us to examine the relationships between possible risk factors and endemic AGE attack rates. Most studies of AGE in leisure settings are reports of norovirus outbreak investigations that may focus on contaminated food and water, but rarely consider the physical characteristics of the setting such as distance to a dining hall, and are usually limited in their time frame. When comparing our results to previous studies, we recognize that many of these outbreak investigations had laboratory-confirmed cases of a specific etiologic agent, whereas this study relies on a case definition based on self-reported symptoms that may be due to both infectious and non-infectious causes. One limitation in comparing results of this study to reported outbreak investigations is publication bias. Literature is more likely to report on studies of outbreaks of AGE and norovirus in leisure settings rather than analyze characteristics of annual attack rates. The medical data from these 22 resorts did not include any recognized AGE outbreaks in 2015, but we were able to characterize AGE cases and examine the effect of various risk factors on AGE attack rates during non-outbreak conditions.

Notable Risk Factors

Attack Rates: Guest versus Staff

One of the most important findings was that guests experienced higher attack rates than staff. This finding is similar to the results from the investigation of the waterborne outbreak in Italy, which reported that 20% of cases were among resort staff (23% in this study) [19]. The investigators recommended that staff members should receive higher incentives to report their illnesses [19]. It is possible that the staff members included in this study were less likely to report illness due to fear of missing work and a lack of incentives to report. However, the resort company had a strict policy for staff to report any symptoms within hours of onset. On the other hand, this difference in attack rates could be attributed to the resorts emphasizing proper hygiene for staff members and their success in preventing person-to-person transmission from guests to staff. Guests may have interacted with each other at a higher rate than with staff members, increasing the person-to-person transmission amongst their own cohort. Further information on the activities of guests during their stay may help explain these results, along with knowledge of the precautions implemented by the resort.

Attack Rate: Onset of Symptoms Relative to the Start of Travel Package

Days later in a travel package were found to have significantly higher attack rates during long stays. While it is a logical conclusion that one case will lead to additional cases during the duration of the resort stay, no previous studies have examined the specific relationship between timing of symptom onset and AGE attack rate in a leisure setting. It is noteworthy that this association was only significant in longer trips, when cases had more time to become exposed to the resort environment and other guests. These results emphasize the need to enact prevention methods, such as case isolation, to prevent further cases, especially during longer travel packages.

Attack Rate: Temporality

AGE temporality observed in these 22 resorts was similar to that reported by a study of AGE on cruise ships where outbreaks were most common during the summer [30]. Overall, summer had the second highest proportion of cases and the highest attack rate (for long stays). This may be due to the overall frequency of short versus long stays during the summer, It is likely that the higher spring-summer attack rates we observed are due in part to an increase in travelers and more crowded travel conditions during the spring and summer months [30]. A review of reported norovirus outbreaks in leisure settings, as well as healthcare, food service, and school/daycare settings, reported significantly higher primary attack rates during winter, after controlling for multiple transmission routes [32]. That report reflects general winter peaks of norovirus, which are in contrast to the spring-summer AGE peak we observed in these resort settings [30].

Attack Rate: Length of Travel Package

There was a significant difference in attack rates between short and long stays. Shorter stays had higher attack rates, an unexpected result. We expected that longer stays would provide more opportunities for exposure to ill guests or staff or environmental contamination. Further research would be useful to better understand this outcome and possible differences in the demographic characteristics of travelers with short stays vs. long stays. To our knowledge, our study is the first to compare AGE attack rates between different lengths of travel packages in leisure settings. Only the AGE surveillance system for cruise ships, maintained by the CDC Vessel Sanitation Program, estimates AGE attack rates over time (per 100,000 travel days) [26]. Most other studies only compare attack rates within a resort at one time.

Attack Rate: Resort Size

Another unexpected finding was between the size of the resort and attack rate. There was a significant, but negative association of size and attack rate for short stays. Even though "very large" resorts had a significantly lower association with attack rate compared to "large" resorts, the "small" resorts had significantly lower attack rates. It is possible that large resorts had greater population density, higher likelihood of the presence of an infected guest or staff member on the premises, and more opportunities for person-to-person contact. No significant associations between resort size and attack rates were observed for short stays, which may be expected to have a weaker association given the time frame. No previous studies appear to have examined the effect of resort size on AGE attack rate, and further investigation into the effects of the geographic size of resorts with high guest occupancy vs. population density on AGE attack rates would be useful.

Attack Rate: Delay in Case Reporting

The reporting of a case later in the travel package was significantly associated with a lower attack rate for both short and long stays. We expected that a delay in case reporting would increase the likelihood that the infected guest or staff member was coming into contact with more people and more likely to infect others at the resort. However, it is possible that the AGE cases were isolating themselves in their rooms before reporting symptoms. Further research into the effect of timely vs. delayed case reporting may help clarify whether there are benefits to provide incentives to guests and staff to report symptom onset as soon as possible.

Overall, the study was successful both in describing the AGE epidemiologic patterns and the associations between certain case and resort characteristics and AGE attack rates in leisure settings. Further information on the demographics of the travelers at these resorts and their behaviors, such as case isolation, would be helpful in interpreting our findings

B: Strengths and Limitations

One of the main strengths of this analysis was the inclusion of a large sample size of over 4,700 cases and 2,475,875 guests and approximately 23,524 staff. A full year of data was available with a recent information on occurrence of AGE cases. The full year was particularly useful to be able to explore variations in AGE seasonality. Additionally, there was a wealth of information on these cases, including age, room number, and specific symptoms and the date of symptom onset. The regression analyses was able to examine the effect of multiple potential risk factors on AGE attack rates.

One limitation of our data was lack of information on AGE etiology because of the inability of the resorts to test AGE cases for specific etiologic agents such as noroviruses. The AGE case definition is based on self-reported symptoms that may be due to multiple causes. Another limitation was the lack of information on whether a case was isolated during the time he/she was symptomatic and other behavior information, such as food eaten or . Information such as age and sex of guests was only known for those reporting illness. Because we did not have information on the demographic characteristics of all the guests and staff, we were unable to calculate age-specific or sex-specific attack rates. There is uncertainty about the size of the staff population during the year. Staff were hired at each resort on an as-needed basis, and therefore staffing levels would fluctuate within a resort throughout the year. The resort was unable to provide specific staff numbers for each travel package and so the staff population was estimated from the company website, which listed number of staff at each resort. While the time frame of a year was useful for examining AGE seasonality, a longer time period would have allowed comparison across multiple years. One limitation in comparing results of this study to reported outbreak investigations is publication bias. Literature is more likely to report on studies of outbreaks of AGE and norovirus in leisure settings rather than analyze characteristics of annual attack rates. The medical data from these 22 resorts in 2015 did not include any recognized AGE outbreaks, but we were able to characterize AGE cases and examine the effect of various risk factors on AGE attack rates.

Chapter 5: Implications/Recommendations

A: Implementing the Results

Without data on foods eaten or isolation practices, the best recommendation for the resort is to focus on the prevention of illness amongst guests. As the results showed higher attack rates amongst guests than staff, the resort should focus on keeping guests healthy. Surveys of guests in a leisure resort found that many either delayed illness reporting or did not report at all if they did not believe it was serious [35]. Guests also did not believe isolation to be effective [35]. Informing guests of AGE symptoms and encouraging reporting of illness and isolation can help reduce attack rates. Illness education could occur during resort tours or information found in guest rooms. Additionally, although no information was collected on foods eaten, ensuring foods are properly cooked can reduce chances of norovirus transmission by food. Encouraging guests to wash hands before eating, and providing them with information on norovirus prevention can also reduce attack rates. Since only 8 of the 5,000 plus cases over 2015 reported having symptoms before arriving at the resort, incentivizing guests to reschedule may not be the most effective method to incentive guests to reschedule their bookings. Although the CDC has suggested routine pre-arrival screening, results from this analysis conclude that prevention methods should target guests that have already arrived [35].

Results from the analysis provide evidence that it is most important to target guests, but staff members may have a higher, unmeasured attack rate. Literature often states that staff may be afraid to seek medical attention due to fear of missing work, and it is possible this fear caused the lower reported attack rate. Therefore, emphasis can be placed on providing more incentives for staff to report symptoms. As found in the literature review, isolation can be one of the best methods for the prevention of person-to-person transmission. By allowing sick staff members to take the appropriate sick leave, the resort can help reduce further cases of both guests and staff.

B: Recommendations for Future Research

Future research on the characterization of AGE in leisure settings should include the use of rapid diagnostic kits to confirm infections, identify asymptomatic infections, and provide information on disease etiology. Other research opportunities include the need for more cohort studies that are conducted during an outbreak rather than follow-up studies. Such studies would provide opportunities to identify outbreak sources and test various intervention strategies, including the length of case isolation and handwashing promotion or monitoring interventions.

Other research needs specific to leisure settings include closer tracking of guest and staff behavior. It would be valuable to know if each case was advised to limit activities and whether or not the cases adhered to isolation suggestions, as well as the proportion of guests and staff that practiced good hygiene, such as handwashing. Other information, such as guest activities, water quality data, and foods consumption patterns would assist in identifying the exposures that increased the risk of AGE in leisure settings. It would also be useful to characterize attack rates by the size of the room or price of the guest room. It is possible that larger and more expensive rooms reduce one's risk of AGE because of less time spent in public spaces of the resort. Another future research topic for leisure settings could be a study of the effectiveness of different cleaning agents and methods in reducing AGE attack rates. For example, no formal analysis has been conducted on the effectiveness of carpet steaming versus wet shampooing versus other techniques to remove or inactivate enteric pathogens [22]. Evidence-based recommendations on effective cleaning methods would likely assist in prevention of AGE outbreaks and decrease attack rates. More research on some of the conflicting results found in this study, such as the higher AGE attack rates associated with short stays versus long stays, would allow better understanding of the relationship between AGE risk and duration of visit and more informed prevention and control strategies.

Through increased research and implementation of evidence-based recommendations, resort settings can become healthier environments for guests and staff. Fewer AGE cases may lead to a decrease in health costs for guests and staff and increased enjoyment of the leisure setting. Overall, investing in the health prevention and better guest and staff care can have large benefits for leisure settings.

References

1. Steffen, R., D.R. Hill, and H.L. DuPont, *Traveler's diarrhea: a clinical review.* JAMA, 2015. **313**(1): p. 71-80.
2. Rockx B, D.W.M., Vennema H, et al. Natural history of human calicivirus infection: a prospective cohort study. Clin Infect Dis. 2002;35(3):246-253.
3. CDC. *Symptoms*. Norovirus 2013 July, 26, 2013 January 19, 2016]; Available from: http://www.cdc.gov/norovirus/about/symptoms.html.
4. Thornton, A.C., K.S. Jennings-Conklin, and M.I. McCormick, Noroviruses: agents in outbreaks of acute gastroenteritis. Disaster Manag Response, 2004. 2(1): p. 4-9.
5. Kirkwood, C.D.a.R.F.B., Molecular detection of human calicivirus in young children hospitalized with acute gastroenteritis in Melbourne, Australia, during 1999. Journal of Clinical Microbiology, 2001. 39(7): p. 2722-4.
6. Caul, E.O., Small round structured viruses: airborne transmission and hospital control. Lancet, 1994. 343(8908): p. 1240-2. .
7. Ho, M.S., et al., Viral gastroenteritis aboard a cruise ship. Lancet, 1989. 2(8669): p. 961-5.
8. Shirato, H., et al., Norovirus and histo-blood group antigens. Japanese journal of infectious diseases, 2011. 64(2): p. 95-103.
9. CDC. *Transmission* Norovirus 2015 January 19, 2016]; Available from: http://www.cdc.gov/norovirus/about/transmission.html.
10. CDC. Diagnosis Treatment 2013 February 20, A.f.h.w.c.g.n.h.d.-t.h.

11. Simons, M.P., et al., *Norovirus: new developments and implications for travelers' diarrhea.* Tropical Diseases, Travel Medicine and Vaccines, 2016. **2**(1): p. 1-7.
12. CDC. *Burden of Norovirus Illness and Outbreaks* Norovirus 2014 July 8, 2014 March 30, 2016]; Available from: http://www.cdc.gov/norovirus/php/illness-outbreaks.html.
13. Treanor, J.a.R.D., eds. Norwalk Virus and Other Caliciviruses. 5 ed. Vol. 2. 2000. 1949-1956.
14. CDC. *Preventing Norovirus Infection* Norovirus 2015 January 19, 2016]; Available from: http://www.cdc.gov/norovirus/preventing-infection.html.
15. Hoffmann, S., Bryan Maculloch, and Michael Batz. Economic Burden of Major, E.-. Foodborne Illnesses Acquired in the United States, U.S. Department of, and E.R.S. Agriculture, May 2015.
16. *Health Protection Scotland, The identification and management of outbreaks of Norovirus infection in tourist and leisure industry settings: guide for NHS boards and local authorities. Joint Working Group Report. (2005) HMSO, Edinburgh*
17. Lawson, H.W., et al., *Waterborne outbreak of Norwalk virus gastroenteritis at a southwest US resort: role of geological formations in contamination of well water.* Lancet, 1991. **337**(8751): p. 1200-4.
18. Brown, C.M., Cann, J. W., Simons, G., Fankhauser, R. L., Thomas, W., Parashar, U. D., & Lewis, M. J. (2001). Outbreak of Norwalk virus in a Caribbean island resort: application of molecular diagnostics to ascertain the vehicle of infection. Epidemiology and Infection, 126(3), 425–432.
19. Boccia, D., et al., *Waterborne outbreak of Norwalk-like virus gastroenteritis at a tourist resort, Italy.* Emerg Infect Dis, 2002. **8**(6): p. 563-8.
20. Migliorati, G., et al., *An outbreak of gastroenteritis in a holiday resort in Italy: epidemiological survey, implementation and application of preventive measures.* Vet Ital, 2008. **44**(3): p. 469-81.
21. Domenech-Sanchez, A., et al., *Unmanageable norovirus outbreak in a single resort located in the Dominican Republic.* Clin Microbiol Infect, 2011. **17**(6): p. 952-4.
22. Cheesbrough, J.S., et al., *Widespread environmental contamination with Norwalk-like viruses (NLV) detected in a prolonged hotel outbreak of gastroenteritis.* Epidemiol Infect, 2000. **125**(1): p. 93-8.
23. Fobert, J. and B.W. Case, *Hospitality Risks: Keeping pace with Emerging Exposures*, A. Group, Editor 2014: Philadelphia, PA.
24. Launders, N.J., et al., *Self-Reported Stomach Upset in Travellers on Cruise-Based and Land-Based Package Holidays.* PLoS ONE, 2014. **9**(1): p. e83425.
25. CDC, *Vessel Sanitation Program* in *2011 Operations Manual* 2011: Atlanta, GA
26. Freeland AL, V.G.J., Banerjee SN. Acute Gastroenteritis on Cruise Ships — United States, 2008–2014. MMWR Morb Mortal Wkly Rep 2016;65place_Holder_For_Early_Release:1–5. DOI: http://dx.doi.org/10.15585/mmwr.mm6501a1.
27. Wikswo, M.E., et al., *Disease transmission and passenger behaviors during a high morbidity Norovirus outbreak on a cruise ship, January 2009.* Clin Infect Dis, 2011. **52**(9): p. 1116-22.
28. CDC, *Acute Gastroenteritis Illness Infographic* 2016: Vessel Sanitation Program

29. Isakbaeva ET, W.M.-A., Beard RS, et al. Norovirus trans- mission on cruise ship. Emerg Infect Dis 2005; 11:154–8. .
30. Cramer, E.H., et al., *Epidemiology of Gastroenteritis on Cruise Ships, 2001–2004.* American Journal of Preventive Medicine. **30**(3): p. 252-257.
31. Hadjichristodoulou, C., et al., *Actions for prevention and control of health threats related to maritime transport in European Union.* Travel Med Infect Dis, 2013. **11**(4): p. 238-42.
32. Hardy, M.A., *Regression with Dummy Variables. Regression with Dummy Variables. SAGE Publications, Inc*. Newbury Park, CA: SAGE Publications, Inc.
33. "North America :: United States." Central Intelligence Agency. Central Intelligence Agency, M.W.A.h.w.c.g.l.p.t.
34. Matthews, J.E., et al., *The epidemiology of published norovirus outbreaks: a systematic review of risk factors associated with attack rate and genogroup.* Epidemiol Infect, 2012. **140**(7): p. 1161-72.
35. Neri AJ, C.E., Vaughan GH, Vinjé J, Mainzer HM. Passenger behaviors during norovirus outbreaks on cruise ships. J Travel Med 2008;15(3):172–6. Available from http://www.blackwell- synergy.com/doi/abs/10.1111/j.1708-8305.2008.00199.x?cookieSet=1&journalCode=jtm. .