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ORIGINAL ARTICLE

Mathematical Modeling of *Vibrio vulnificus* Infection in Korea and the Influence of Global Warming

Chaeshin Chu [a], Younghae Do [b], Yongkuk Kim [b], Yasuhisa Saito [b], Sun-Dong Lee [c], Haemo Park [c], Jong-Koo Lee [d,*]

[a]*Division of Epidemic Intelligence Service, Korea Centers for Disease Control and Prevention, Osong, Korea.*
[b]*Department of Mathematics, Kyungpook National University, Daegu, Korea.*
[c]*Department of Preventive Oriental Medicine, Sangji University, Wonju, Korea.*
[d]*Korea Centers for Disease Control and Prevention, Osong, Korea.*

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Abstract

Objectives: To investigate the possible link between *Vibrio vulnificus* population size in seawater and water temperature.
Methods: We collected incidence and water temperature data in coastal regions of Korea and constructed a mathematical model that consisted of three classes; susceptible fish, infected fish available to humans, and infected humans.
Results: We developed a mathematical model to connect *V. vulnificus* incidence with water temperature using estimated bacterial population sizes and actual coastal water temperatures.
Conclusion: Increased *V. vulnificus* population sizes in marine environments may increase the risk of infection in people who eat at coastal restaurants in Korea. Furthermore, we estimated the near-future number of infected patients using our model, which will help to establish a public-health policy to reduce the disease burden.

1. Introduction

Global warming is accompanied by an increase in the frequency of extreme weather events such as heat waves, floods, and droughts [1,2]. Such climate change can also impact on the spread of infectious diseases [3,4]. For example, a rise in sea surface temperature in a given area can be followed by an increase in the number of people infected with cholera [5].

Water- and food-borne diseases are a major cause of mortality worldwide and an important cause of morbidity in both developing and developed countries [6]. Most cases

*Corresponding author.
E-mail: docmohw@korea.kr

of water-borne and food-borne gastroenteritis, particularly infections caused by *Campylobacter* and *Salmonella*, exhibit a distinct summertime pattern of occurrence [7]. This association between warmer temperatures and disease suggests that rates of water- and food-borne illnesses are likely to increase with rising temperatures [6].

Globally, the water-borne enteric disease that is most likely to increase in the face of global climate change is cholera. This is a diarrheal disease with a high case-fatality rate caused by infection with toxigenic *Vibrio cholerae* strains, and remains an important cause of death in the developing world [6]. Nontoxigenic strains of *V. cholerae* and other noncholera *Vibrio* spp., including *Vibrio parahemolyticus* and *Vibrio vulnificus*, may also become more frequent agents of disease because of increasing ocean temperatures and increasing frequency of extreme weather events [6]. For example, cases of illness due to these microorganisms occurred in association with Hurricane Katrina in 2005 [7].

V. vulnificus is a naturally occurring, free-living bacterium that inhabits estuarine and marine environments throughout the world, residing in high numbers in filter-feeding shellfish [oysters, clams, and mussels] [8]. *V. vulnificus* is distinguished from other members of the *Vibrio* genus in its ability to ferment lactose, and its presence in the estuarine environment is not generally associated with pollution or other forms of contamination. Under certain conditions this bacterium has the ability to cause serious and fatal infections. These include an invasive septicemia, usually contracted through the consumption of raw or undercooked shellfish, as well as wound infections acquired through contact with shellfish or marine waters where the organism is present [9].

The number of people infected worldwide with *V. vulnificus* is low when compared with other *Vibrio* species, but it is responsible for a significant percentage of *Vibrio*-related illnesses in the United States [10]. Furthermore, the severity of disease resulting from infection with this species potentially makes it the leading cause of seafood-associated fatalities in the US [11,12].

V. vulnificus was recognized as a distinct species in the 1970s, when it was realized that many clinical cases of food-borne septicemias and wound infections were caused by a pathogen with characteristics unique from other *Vibrio* spp. [12]. It is one of the most fatal waterborne bacterial pathogens, with a case-fatality rate that may reach 50% for *V. vulnificus* septicemia [7]. Microbiological studies have shown that the bacterium is highly sensitive to water temperature and salinity, proliferating in areas where water temperature exceeds 20°C [13]. This habitat preference explains its seasonality and geographic distribution [14,15].

V. vulnificus prefers tropical to subtropical climates, and has been isolated from waters where temperatures range from 9°C to 31°C. Low to moderate salinities are also associated with the presence of this species. Although it has been isolated from waters with one part per thousand (ppt) to 34 ppt salt concentration, the normal range for *V. vulnificus* is 15−25 ppt [15]. Salinities greater than 25 ppt have an adverse effect on survival [16,17]. Changes in total numbers of viable *V. vulnificus* cells present in any location are further associated with the ambient water temperature. At temperatures below 10°C, the number often drops to nearly undetectable levels [13,18].

Estuarine fish species may also serve as a reservoir for transport of this bacteria species between oyster beds, or as a source of wound infections [9]. In oysters, *V. vulnificus* resists depuration and other chemical disinfection methods typically used to eliminate enteric pathogens [19]. Cooking shellfish is currently the only reliable method to completely destroy the bacterium.

The global epidemiology of *V. vulnificus* suggests a recent emergence. Since its recognition as a human pathogen in the 1970s, cases of infection have been reported from many parts of the world, including Korea [9]. Almost all reported cases of primary septicemia and gastroenteritis were preceded by consumption of raw shellfish [20]. Other cases appear to have involved the consumption of raw clams and cooked shrimp, although most of the reported cases of *V. vulnificus* gastroenteritis also involved eating raw oysters [20].

Contact with water or shellfish in areas or during seasons of high *V. vulnificus* prevalence was reported in most of the cases of *V. vulnificus* wound infections. Many wound infections appear to be related to occupational exposures among oyster shuckers and commercial fisherman, with 69% reporting either fishing or handling raw seafood during the 7 days preceding illness [9].

In the Gulf Coast survey, preexisting conditions were more common among patients with primary septicemia (97%) than those with wound infections (68%), whereas only 35% of patients with *V. vulnificus* gastroenteritis were identified as having any of these predisposing factors [20]. There was less of a correlation with any specific risk factor and susceptibility to *V. vulnificus*-caused gastroenteritis. Overall, liver disease was the most common risk factor in those who contracted primary septicemia, which was present in up to 80% of those infected. Wound infections occurred more often in people with at least one predisposing condition other than liver disease.

The Korean government has designated *V. vulnificus* infection within the Notifiable Diseases Group 3 since 2000 and physicians who detect infected patients are required to report cases to local health authorities, and eventually to the Korea Centers for Disease Control and Prevention (KCDC) within three days. Incidence of this infection in Korea includes 41 cases in 2001, 60 cases in 2002, 80 cases in 2003, 57 cases in 2004, 57 cases in 2005, 88 cases in 2006, and 58 cases in 2007 [21]. Raw consumption of fish is common in both coastal and inland areas of Korea, and increases the risk of infection.

The raw fish restaurants in coastal areas use natural saline seawater, whereas the inland raw fish restaurants use temperature controlled seawater. Most reported patients are male residents from coastal areas who eat raw fish and have renal disease, with infection occurring during August and September [21].

In view of the severe disease manifestation caused by *V. vulnificus,* characterized by progressive inflammation of soft tissues and rapidly progressing erythema, cellulitis and necrosis, it is unlikely that recognition of this infection was delayed because of an underreporting of disease cases [22]. Given the organism's dependence on temperature, it is reasonable to speculate that changes in the water temperature in the coasts may have altered the levels of *V. vulnificus* populations in the water, consequently increasing the risk of human infection [23]. Recent study further shows that Korea is under influence of global warming, thereby increasing the risk of emerging infectious diseases [24].

Based on these observations, this study aimed to analyze the *V. vulnificus* infection trend from a new viewpoint: assessment of the possible regional impact of global warming on Korean coasts has on water temperature using mathematical modeling.

2. Materials and Methods

2.1. Research area

To determine the spread of *V. vulnificus* in Korea, especially in relation to climate change, the present study focused on the water temperature of Korea. For the last 35 years, the average water temperature surrounding the Korean coast has increased by 0.7°C. We therefore investigated the possible link between the changes in marine *V. vulnificus* population levels and water temperature.

Korea is surrounded by three coastal regions, of which the south and west coasts were chosen for this study (Figure 1). These areas were selected because more than 95% of reported infections occurred within these coastal locations and 90% of the patients resided in these areas in 1990s [21]. To examine the spread of *V. vulnificus* along the west coast, we choose two representative locations: Incheon [37°26′57″N, 126°35′39″E] and Mokpo [34°46′36″N, 126°22′39″E]. Compared with other western coastal cities, many *V. vulnificus* cases in these two areas were reported after 2000. For the south coast, we also choose two representative locations with high incidence: Wando

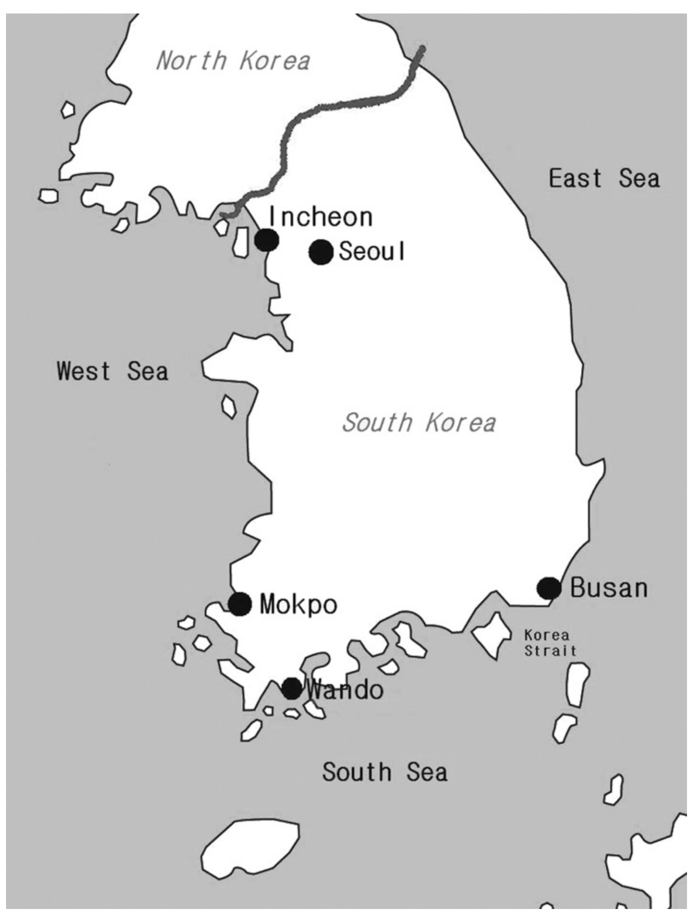

Figure 1. Four representative test locations are indicated on the map of Korea.

(34°18′45″N, 126°45′41″E) and Busan (35°05′30″N, 129°02′15″E).

In this study, we used water-temperature data collected for the four above-mentioned locations more than 7 years (from 2001 to 2007) by the National Oceanographic Research Institute [25]. Analysis of this water-temperature data revealed that the average number of days with water temperature more than 20°C has increased from 2003 to 2007 (Figure 1). This implies that *V. vulnificus* populations are potentially spreading, because this species can rapidly propagate water environments with temperatures more than 20°C.

2.2. Mathematical model

To illustrate the relationship between *V. vulnificus* infection and global warming, predict a future trend for *V. vulnificus* incidence, and facilitate the drafting of a Korean government public health policy for reducing *V. vulnificus* incidence, we constructed a prototype model that consisted of three classes; susceptible fish, infected fishes available to humans, and infected humans. This model assessed the relationships between these three classes and the impact water-temperature variation has on *V. vulnificus* populations. Details of our model are given in the Appendix.

Within the mathematical process used to formulate our model equations, among other assumptions, we assumed for simplicity that the size of a bacteria population is 0 when the water temperature is less than 20°C, because bacterial population sizes are quite small when the water temperature is less than 20°C compared with those when the water temperature is more than 20°C. Because of an absence of the data of *V. vulnificus* population versus water temperature from Korean coastal areas, we used data recorded at Barnegat Bay [8], because of similarities, especially in water temperatures, between this location and the coasts of Korea. Finally, we derived a function for the relationship between *V. vulnificus* population size and water temperature using a general regression method. See Appendix for the relationship between these factors.

2.3. Numerical computation

To conduct a numerical simulation for our model, we used actual water-temperature data recorded by the National Oceanographic Research Institute from 2001 to 2007. Based on the Runge-Kutta scheme, we numerically calculated *V. vulnificus* incidence. To estimate the values of the parameters used in our model, we tested many simulations in random parameter settings and then deduced the appropriate parameters by comparing the result of numerical simulation with the number of annual cases of *V. vulnificus* infection in KCDC from 2001 to 2007. To predict the future number of cases of this infection, we increased water temperature by 0.02°C per year, successively adding to the water temperature recorded in 2007, as 0.02°C is the average increase of water temperature along the Korean coast.

3. Results

In the KCDC 2007 Annual Report [21], most of the infected patients were reported between June and October, with most of these being male (91.0%) and older than 40 years (90.2%). The outbreak season for *V. vulnificus* infection is characterized by water temperature more than 20°C along the Korean coast. As shown in Figure 2, the number of days with water temperatures more than 20°C in the south- and west-coastal regions with high incidence of infection has tended to increase since 2003. Such an increase may be the result of global warming, given that the average temperature of Korean coastal waters has increased by 0.7°C for the last 35 years. This may subsequently affect the spread of *V. vulnificus.* The correction between the number of days with water temperature more than 20°C and the changing average water temperature of the local environment is shown in Figure 3. The number of days with water temperature more than 20°C was sensitive to small changes in the average water temperature, implying that increased spread of *V. vulnificus* could potentially occur as a consequence of global warming.

For numerical modeling predications, we measured the population size of bacteria $B(t,T)$ against the water temperature. For example, Figure 2 shows the population size of bacteria versus the water temperature measured in the Busan area at 2002 under our hypothesis. That is, the population size of bacteria is zero if the water temperature is less than 20°C. Using the bacteria's population size obtained from the real water temperature, we can then calculate the predicted population size of people infected by *V. vulnificus*.

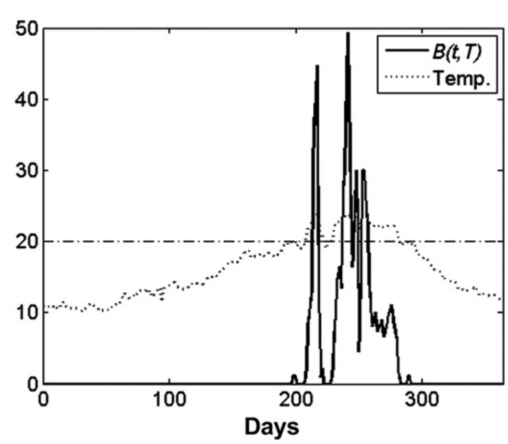

Figure 2. The dashed line indicates the actual water temperature measured in Busan in 2002 and the solid line represents the population size of bacteria at time t and temperature T. The dash-dot line denotes a water temperature of 20°C.

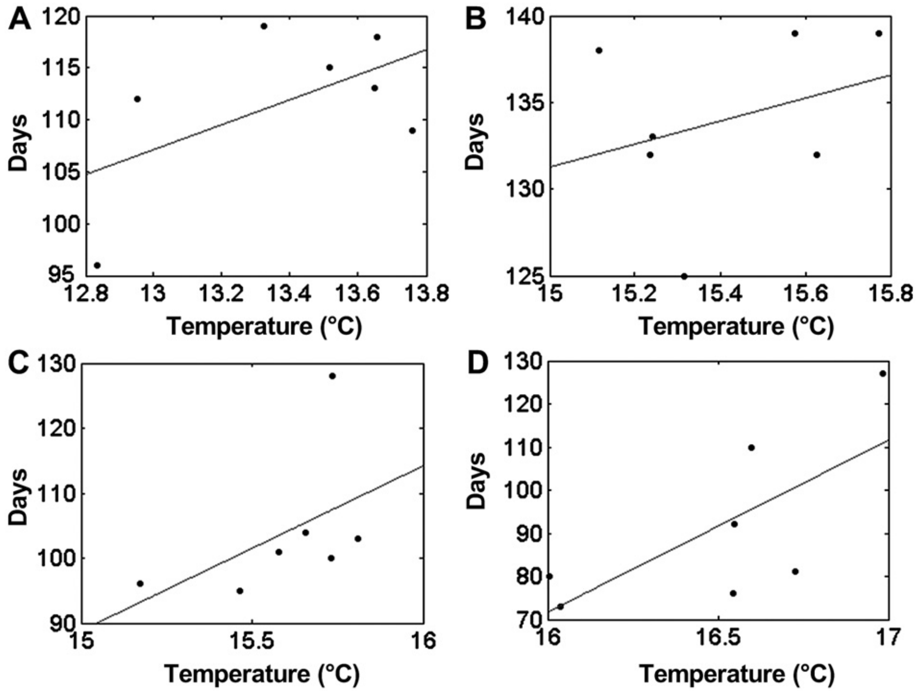

Figure 3. The number of days with water temperature more than 20°C versus the average water temperature observed in (A) Incheon, (B) Mokpo, (C) Wando, and (D) Busan. Solid lines were obtained from the linear regression.

To obtain realistic parameters needed for the simulation of our mathematical model, we tested several random parameter settings and the real data of the water temperature of Busan, Wando, Mokpo, and Incheon. Finally, we fixed the parameters as $\alpha = 0.002$, $\beta = 0.01$, $\alpha' = 0.01$, $\beta_{\mathrm{H}} = 3 \times 10^{-11}$, $q = 10$, $A = 0.6$, and then compared our numerical result with the actual data from 2001 to 2007. Our model computed a curve that closely fluctuated around the real incidence data from 2001 to 2007 (Figure 5), supporting the predictive potential of our algorithm.

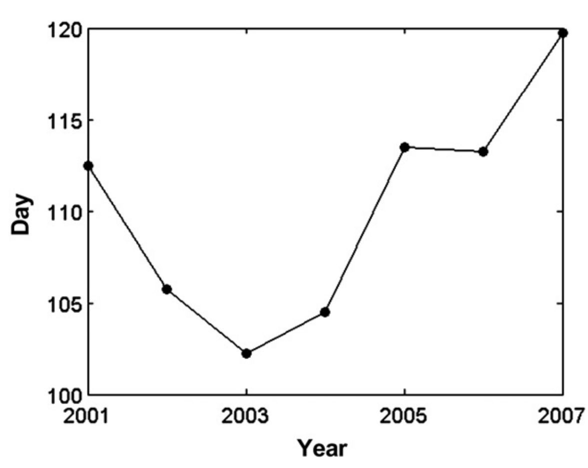

Figure 4. Average number of days with water temperature more than 20°C observed in four coastal areas: the south coast (Busan and Wando), and the west coast (Incheon and Mokpo) from 2001 to 2007.

To understand the effect of global warming on *V. vulnificus,* we assumed that the water temperature obtained in 2007 for the four tested locations would constantly increase by 0.02°C each year, which is the average increase in water temperature for the past 35 years [26]. Under the same parameter settings, we considered the data for water temperature measured from the four study locations, which are situated in major costal areas of Korea and calculated *V. vulnificus* incidence. An increased rate (p%) of incidence of *V. vulnificus* infection was observed (Figure 6). This suggested that the incidence would increase almost

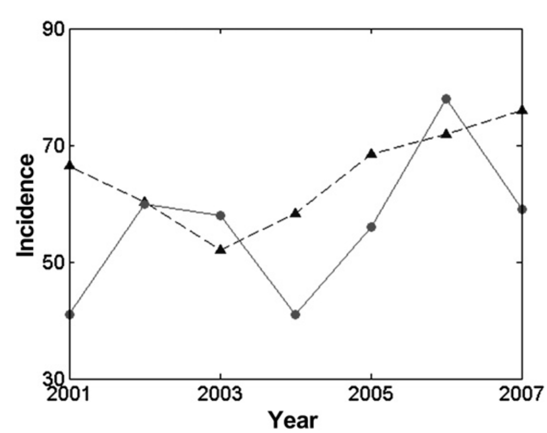

Figure 5. The filled circles indicate the incidence of *V. vulnificus* infection reported from 2001 to 2007 and the filled triangles were obtained from the simulation results of our model.

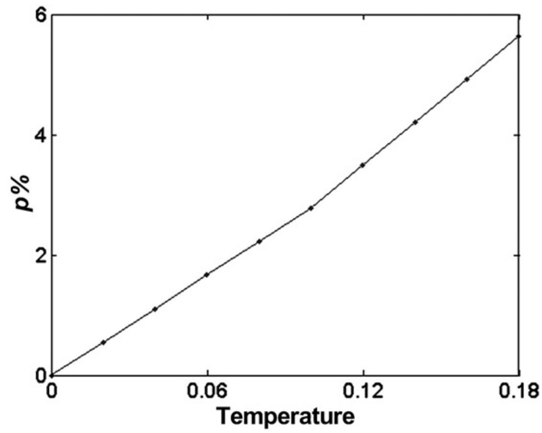

Figure 6. Increasing rate (*p*%) of incidence of *V. Vulnificus* infection versus water temperature.

linearly as temperature increases within a certain range, thus indicating that temperature is an important factor for the increased expansion of this infectious disease.

Our model-based simulation result also showed that *V. vulnificus* incidence increased with an increase in water temperature Figure 4. This suggests that changing environmental factors may dramatically affect the epidemical spread of a disease, and water temperature appears to be directly linked to the levels of *V. vulnificus* infection. Our model is based on the idea that water temperature affects the growth of *V. vulnificus* in coastal waters and coastal seafood restaurants that use aquariums filled with raw seawater. Thus, the number of bacteria in infected fish is directly related to the number of persons infected by consuming raw fish, as indicated by the real incidence of infection from 2001 to 2007 fluctuating around the modeled predications.

4. Discussion

Although many bacteria species are sensitive to water temperature, the relationship between bacteria and water temperature from a previous study [8] cannot be utilized because of differences in the topology of Korea. We therefore have successfully developed a model to assess this relationship using data specific for Korea that indicated a significant association between infection and the number of days of water temperature more than 20°C (Figure 1). The number of days with warmer temperatures is an important climatic factor encouraging the appearance of the disease, because it increases the chance of consuming infected raw fish.

A study on *V. vulnificus* population dynamics also reported the influence of salinity [8], which we further checked using data from the west coast of Korea. Salinity levels at two sites along the west coast were lowered to 17−25 parts per million during the summer (July−September), which appears to be favorable for the growth of the bacteria and to explain the relatively high incidence in these areas. Such changes in salinity are caused by these areas being located near estuaries of major rivers in Korea, along with the reduction in levels observed during the rainy season. Unfortunately, more specific data were not available, and we were consequently unable to include salinity parameters within our model.

The major consumers of raw fish are males aged more than 40 years old, with most of these individuals also likely to consume alcoholic beverages. When coupled with renal syndrome, *V. vulnificus* infection considerably increases disease fatality [21]. Therefore, the habit of eating raw fish by Korean males who drink alcohol is a risk factor for increased infection and fatality. Consequently, education of costal residents about the risk factors of infection is important to reduce the incidence of the disease is essential [21].

Climatic modeling projects are likely to continue to rise in the next decades, given the effects of greenhouse gases and aerosol emissions on global temperature. Such changing climatic conditions will also potentially increase water temperature and salinity, thereby increasing the chances of *V. vulnificus* infection in Koreans who reside in coastal areas. Furthermore investigation is necessary using larger temperature and salinity datasets.

5. Conclusions

Increased *V. vulnificus* populations in the water may heighten the risk of infection in people who dine at coastal restaurants in Korea that use natural saline seawater aquariums for seafood. Furthermore, our model allows for estimates to be made on the number of people likely to become infected with this bacteria species in the near future. This will also help to establish a public health policy to reduce disease burden. Although our model provides a strong basis to predict *V. vulnificus* infection levels, further application of the model requires additional data on relevant *V. vulinificus* numbers in seafood associated with infection at the point of consumption, and further characteristics of the susceptible population.

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Appendix: Mathematical Modeling

Let τ be the period of a year and t be the time variable. Each year should be divided into two parts in terms of temperature T as follows:

$$0 \le t < t_1 \text{ for } T < 20$$

$$t_1 \le t \le t_2 \text{ for } T \ge 20$$

$$t_2 < t < \tau \text{ for } T > 20$$

We assume that there is no possibility that fish can be infected with *Vibrio* bacteria in the case $T < 20$, since the population size of the bacteria is quite small. Thus, we should only consider the case:

$$t_1 \le t \le t_2 \text{ for } T \ge 20$$

We made a model to describe the *Vibrio* problem by using the following variables: $F^S(t)$ is the population size of susceptible fish available to human at time t; $F^I(t)$ is the population size of infected fish (available to human) at time t; F is the total population size of fish, $F^S(t) + F^I(t)$, which is assumed to be constant for simplicity.

$B(t, T)$ is the population size of bacteria at time t and temperature T; where we assume $B(t, T) = 0$ for all t if $T < 20$ and adopt for the case $T \ge 20$ that

$$B(t, T) = \begin{cases} \exp(T - 20) & \text{if } 20 \le T \le 26 \\ \exp(-(20/26)T + 26) & \text{if } T > 26 \end{cases}$$

referred from a paper [8]. For instance, Figure 3 represent the relation between water temperature and $B(t, T)$.

$H^I(t)$ is the population size of human having been infected until time t; H is the total population size of human willing to eat fish, which is assumed to be constant since $H^I \ll H$.

Assume that the per capita consumption of human willing to eat fish on average is written in the form αF, where α is the rate by which human eats fish, and that the human does not know whether the fish is infected or not. Under these assumptions set up as above, the model equations are expressed as follows:

$$\frac{dF^S}{dt} = (1-c)\alpha HF - \beta\alpha' B(t,T]\, F^S - \alpha HF^S$$

$$\frac{dF^I}{dt} = c\alpha HF + \beta\alpha' B(t,T]F^S - \alpha HF^I$$

$$\frac{dH^I}{dt} = \beta_H \alpha HF^I$$

with initial data

$$F^S(t_1) = F, F^S(t_1) = 0,\ FH^I(t_1) = 0.$$

To determine the fish input, $(1-c)\alpha HF$ and $c\alpha HF$, related to the water temperature, we introduce a kind of the switching function with respect to temperature of the form:

$$c = c(T) = \frac{1}{1+\exp\left[-2\left(\frac{T-22.5}{q}\right)\right]}, \quad (1)$$

where q represents the sensitivity of the curve around $T = 22.5$. If we determine the system input with Eq. (1), we can describe the way that the input $c\alpha HF$ is so small at first, begins to increase when temperature approaches 20, but quickly increases between the temperature is 20 and 25 to become 1 at $T = 25$ with some appropriate q. Here, α' is the encounter rate between fish and bacteria, and β is the infection rate of fish caused by bacteria, and β_H is the infection rate of human caused by infected fish.

Fortunately, the equations can be solved. From the first equation in the model by using the method of constant variation, we have an exact form of $F^S(t)$ as

$$F^S(t) = \left[F + \int_{t_1}^{t} (1-c)\alpha HF e^{\int_{t_1}^{s} \beta\alpha' B(u,T)+\alpha H \mathrm{d}u} \mathrm{d}s\right] \times e^{-\int_{t_1}^{t}[\beta\alpha' B(s,T)+\alpha H]\mathrm{d}s} \quad (2)$$

For $t_1 \leq t \leq t_2$. By substituting the above equation into the F^I's equation in the model and again using the method of constant variation on the resulting equation, we obtain

$$F^I(t) = e^{-\alpha H(t-t_1)} \times \int_{t_1}^{t} \left\{ c\alpha HF + \beta\alpha' B(s,T) \times \left[F + \int_{t_1}^{s} (1-c)\alpha HF e^{\int_{t_1}^{u}(\beta\alpha' B(v,T)+\alpha H)\mathrm{d}v} \mathrm{d}u\right] \times e^{-\int_{t_1}^{s}(\beta\alpha' B(u,T)+\alpha H)\mathrm{d}u} \right\} e^{\alpha H(s-t_1)} \mathrm{d}s$$

for $t_1 \leq t \leq t_2$. Therefore, we get

$$H^I(t_2) = \int_{t_1}^{t_2} \beta_H \alpha HF^I(s)\mathrm{d}s \quad (3)$$

By the definition of H^I, the value Eq. (3) means the number of human having been infected until time t_2, which we want to know and should fit real data on the *V. vulnificus* infection patients within each year.