Modeling an Outbreak of Anthrax

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On October 2, 2001 a 63-year old Florida man who worked as a photo editor in a media publishing company was admitted to an emergency department complaining of nausea, vomiting and fever. His symptoms began four days earlier on a recreational trip to North Carolina. The man died shortly thereafter. An astute clinician quickly made the surprising diagnosis of inhalational anthrax which is a serious and deadly disease. The diagnosis was surprising because inhalational anthrax is extremely rare and in fact only 18 cases were reported in the United States between 1900 and 1978. Public health officials at first believed that the Florida case was an isolated rare event that might have gone unnoticed except for the heightened state of public health vigilance and alert following the catastrophic events of September 11, 2001. However, when a second case occurred in a 73 year old man who worked at the same Florida media publishing company and delivered mail to the first man, the coincidence seemed remarkable. Employees of the media publishing company reported seeing a suspicious letter on or about September 19, 2001 although that letter was never found. Public health officials theorized that a letter contaminated with deadly finely milled anthrax spores was the source of the disease. Thus, began the 2001 anthrax outbreak in the United States caused by the intentional release of anthrax spores, an act of bioterrorism.

Anthrax is caused by the bacteria bacillus anthracis. There are three types of anthrax. Gastrointestinal anthrax is caused by eating contaminated meats. Cutaneous anthrax is transmitted through the skin. Inhalational anthrax is the most serious form with the highest mortality rate and is transmitted when anthrax spores are inhaled deep into the lungs where they may germinate producing toxins. Inhalational anthrax is of most concern to public health and law enforcement officials because of its potential as a biological weapon. Although anthrax is not transmitted person to person, anthrax spores have the potential to be turned into an aerosol and disseminated widely through the air causing widespread disease. Antibiotics can prevent disease in persons who inhaled spores provided the antibiotics are circulating in the body when a spore begins to germinate.

Following identification of the two cases in Florida, public health officials closed the media publishing company and treated over 1100 employees with antibiotics. On October 9, a letter addressed to Senator Dashle was processed at the Hamilton post office in New Jersey. The letter was then sent to the Brentwood post office in the Washington, D.C. and ultimately to the Hart Senate Office building. When a clerk opened the letter, a puff of white powder spread deadly anthrax spores through the air. The building was immediately closed and workers were treated with antibiotics to prevent disease. At the time, it was not completely clear to public health officials that the tiny anthrax spores were smaller than the pores of an envelope and thus the spores could seep through a sealed envelope putting at risk all persons who came in contact with the letter before it was even opened. After postal workers at the Hamilton postal facility in New Jersey and the Brentwood facility in Washington became ill, all postal workers at these facilities were treated with antibiotics to prevent disease and the buildings were closed.

While there were ultimately only 11 cases of inhalational anthrax nationwide in the 2001 U.S outbreak including 5 deaths, over 10,000 persons were treated with antibiotics to prevent disease. None of the persons who received antibiotics came down with the disease. An important public health question concerns whether cases of disease were actually prevented by the use of antibiotics? How big could the outbreak have been? Was the public health measure of giving antibiotics to exposed persons effective? Unfortunately there is relatively little direct data available to answer these questions. However, statistical models can help fill in the gaps of knowledge and tell the story of what happened and what could have happened.

The Iceberg Phenomenon

A model can be developed to help answer the question, how many cases of anthrax were prevented by the antibiotics. The key idea is what we call the iceberg phenomenon. The cases that are symptomatic and come to public attention may only be the tip of the iceberg, as there may be many other potential cases that are also infected but their disease is still incubating. These cases, the one below the tip, are the silent cases that have not yet become symptomatic. The iceberg phenomenon is illustrated in Figure 1. The question is can we estimate the entire size of the iceberg from just the tip?

A common source outbreak is one in which the time and location of the exposure to the infectious agent is the same for all affected cases. When anthrax spores are disseminated into the air it is believe that they remain suspended for at most one day during which time they have the potential to be inhaled into a persons lungs. The clusters of anthrax cases in the New Jersey, Washington postal facilities and the Florida media publishing company can be considered common source outbreaks.

The time from when a person is exposed to an infectious agent and the onset of symptomatic disease is called the incubation period.

Let’s consider a simple numerical example. Suppose 4 cases of disease occur within 11 days of exposure in a common source outbreak. Let’s also suppose that the median incubation period is 11 days, that is , the probability is half that the incubation period is smaller or equal to 11 days and half that it is greater than 11 days. Thus the 4 symptomatic cases that occurred in the first 11 days following exposure to the infectious agent should represent only about half the total cases as the other half are still incubating, Therefore, based on the size of the tip of the iceberg which is 4 cases and the incubation period, we estimate that the entire iceberg is about 8 cases.

The cases of disease that initially occur when an outbreak begins to unfold are the cases with the shorter incubation periods. There may be many other persons who are also infected but their disease has not yet produced symptoms. Thus, a central idea underlying the iceberg effect is that there is variability in incubation periods and that incubation periods follow a probability distribution. The probability distribution of the incubation period $F(t)$ is the probability that the incubation period is less than t days. To illustrate the notation, $F(11) = .5$ means that the probability is .5 that an incubation period is less than 11 days. We shall define $F(t)$ only among persons who received sufficient dose of the infectious agent to ultimately become ill with symptoms, and as such $F(t)$ is a proper distribution function, that is, $F(t)$ eventually approaches 1 after sufficient time has elapsed. In general, suppose X cases of disease occur within t days of the exposure in a common source outbreak. We would like to estimate the total number of cases that would eventually occur which is called N. The X cases are just the cases with incubation periods shorter than t days and are the tip of the iceberg. We can estimate the entire size of the iceberg N from the equation $F(t) \approx X/N$ if we had knowledge of the incubation period and specifically the value of $F(t)$. Thus, $N=X/F(t)$.

To illustrate these ideas, suppose the incubation period distribution is $F(t) = 1\text{-}e^{-.o7\,t,}$ which is an example of an exponential distribution. Suppose in a common source outbreak we observe 10 cases of disease within 7 days following the exposure. We would expect only about 39% of incubation periods to be less than 7 days because $1\text{-}e^{-.o7\,x\,7} = 0.39$. Thus, the total number of cases we would eventually expect to see in this entire outbreak is about 26 because $N \approx 10\,/.39 \approx 26$.

The Incubation Period of Anthrax

If we want to gain understanding about the anthrax outbreak from the iceberg phenomenon we need to know something about the incubation period of the disease. There is some experimental data from monkeys but very little data about the incubation period in humans. The largest human outbreak occurred in the city of Sverdlosvk, Russia that is about 900 miles east of Moscow in April 1979 (Meselson, Guillemin, Hugh-Jones, et al.., 1994; Guillemin, 1999). Some public officials initially suggested that the Sverdlosvk outbreak was of the gastrointestinal type that resulted from eating contaminated meat. However epidemiological investigation showed that the Sverdlovsk cases lived or worked in a narrow geographical band consistent with wind directions. Pathological reports also indicated that the outbreak was inhalational anthrax. Ultimately Soviet officials confirmed that the outbreak occurred because of an accident at a military microbiology research facility in which a vent was accidentally left open on April 2, 1979 causing the dispersal of anthrax spores into the air. Soviet public health officials attempted to control the outbreak by distributing antibiotics and vaccine to exposed persons in Sverdlosvk. However, it is not known how many persons received antibiotics or vaccine, for how long, nor the effectiveness of these antibiotics and vaccines.

It is believed that spores fall to the ground within one day and do not generally resuspend into the air, and thus it can be assumed that the Sverdlosvk outbreak was a common source outbreak with exposure date of April 2. 1979. A histogram of the incubation periods of 70 cases from the Sverdlosvk outbreak shows a long tail with incubation periods as long as 40 days. Can we obtain a credible estimate of the incubation period distribution from this data? An important caveat with a naïve analysis of the data in is that cases destined to have long potential incubation may be less likely to be included in the data set for the following reason. It took about two weeks following the accidental release of the anthrax spores for public health officials to begin disseminating antibiotics and vaccine. Thus, only persons with potential incubation periods greater than two weeks would have had an opportunity to obtain antibiotics and perhaps have their disease prevented. Thus a naïve analysis of the data might underestimate the true incubation period distribution because it might preferentially exclude some of the cases with long incubation periods. Statisticians call this phenomenon right truncation, a form of selection bias that occurs when larger observations may be less likely to be included in the data set.

A statistical model can help adjust the data for the bias introduced by right truncation. For example, it could be assumed that all cases who became symptomatic prior to the start of the public health control measures are included in the data set but only a random sample of cases with potential incubation periods beyond the start of the public health control program are included in the data set because disease in the remaining persons was prevented. That assumption together with an assumed functional or parametric form for the incubation period distribution is sufficient to adjust the data for the bias introduced by right truncation. Sartwell (1950) pioneered the use of the lognormal distribution for the incubation distribution of infectious diseases. The distribution is lognormal if the logarithm of the incubation period follows a normal distribution, that is, a logarithmic transformation produces the familiar bell-shaped curve. The lognormal distribution is right skewed which means that it has a long right tail. An analysis that used the data from the Sverdlovsk outbreak, the lognormal distribution and a correction for the bias introduced by right truncation, showed that the median incubation period was about 11 days (Brookmeyer, Blades, Hugh-Jones, and Henderson, 2001). The incubation period distribution based on this analysis is illustrated in Figure 2.

Statistical Model for the 2001 U. S. Anthrax Outbreak

The 2001 U.S outbreak of inhalational anthrax occurred principally in three clusters: two cases that occurred in the Florida media publishing company, two cases among the postal workers exposed at the Hamilton postal facility in New Jersey and four cases among the postal workers at the Brentwood postal facility in Washington D.C. (Jernigan, Stephen, Ashford et al., 2001). In total, 8 cases of inhalational anthrax occurred from these three clusters. The data that is available for analysis, illustrated in Figure 3, shows the dates of onset of symptomatic disease among the cases, the dates antibiotics were distributed to all people in the cluster, and the dates persons were exposed to the letter containing the anthrax spores in New Jersey and Washington. The date of exposure is unknown in the Florida cluster because that letter was never found.

The total number of cases that could have occurred in the New Jersey and Washington clusters can be estimated by using the iceberg phenomenon provided there is an independent estimate of the incubation period distribution such as that derived from the Sverdlovsk outbreak. The statistical model used to describe the number of cases that occurred in each cluster is the binomial distribution. The sample size parameter of the binomial distribution, N, represents the total size of the iceberg and is a parameter which is estimated. The "success" probability of the binomial distribution is the probability that the incubation period is less than the time interval between exposure to the infectious agent and when antibiotics were distributed. The modeling is a little more complicated for the Florida cluster because the date of exposure is uncertain, and so an additional parameter needs to be introduced into the model which is the calendar date the Florida cases were exposed to the letter contaminated with anthrax spores (Brookmeyer and Blades 2002; 2003).

The parameters of the statistical model were estimated using maximum likelihood methods. The maximum likelihood method is a statistical procedure to find estimates of the model parameters that are most consistent with the observed data. The results of the analysis are summarized in Figure 4 which shows the profile likelihood (normalized to one) for the total number of cases from all three clusters that would have occurred if not for the use of antibiotics. The profile likelihood is a useful graphical display of the evidence for how big the outbreak could have been. The likelihood function shows which values of N are best supported by the data. The mode of the profile likelihood in Figure 4 is N=17 cases. Thus, while only 8 cases of inhalational anthrax actually occurred in these three clusters, it is estimated that potentially there could have been 17 cases, suggesting that the public health control campaign to distribute antibiotics halved the number of cases. The date that the letter contaminated with anthrax spores arrived at the Florida publishing company estimated by the statistical analysis was September 18, 2001, only one day earlier than when employees reported seeing that suspicious letter.

Quantifying Uncertainty

Describing uncertainty in estimates from a model is an important component of a thorough analysis. The profile likelihood shown in Figure 3 not only displays the "best" estimate but also visually communicates uncertainty in that estimate. The estimate of the total number of cases that could have occurred was 17, but there is uncertainty in that estimate. The 95% confidence interval accounts for statistical error by giving a range of plausible values for N and the confidence interval was between 10 and 28 cases.

However, that confidence interval does not actually account for all sources of uncertainty. It reflects only uncertainty due to sampling variation, and does not account for possible errors in the underlying model assumptions. For example, one underlying model assumption is the incubation period distribution. The incubation period was estimated from the Sverdlovsk outbreak, which are subject to both sampling and non-sampling errors. One way to address these additional sources of error is to perform a sensitivity analysis to different assumptions about the incubation period. For example, if the median incubation period is assumed to be 17 days instead of 11 days, then the potential size of the outbreak would have been 34 cases instead of 17 cases. If longer incubation periods, are used in the statistical model, then the estimates of the numbers of cases that were prevented becomes larger. Intuitively that happens because if the incubation period is longer, more cases are incubating and thus the tip of the iceberg is a smaller part of the entire iceberg. Even with extreme assumptions about the incubation period distribution, the estimates of the potential size of the outbreak were always less than about 50 cases.

Another source of error concerns the statistical procedure itself. For example, the procedure that produced a confidence interval for N was an asymptotic procedure (actually called a likelihood ratio based confidence interval procedure). An asymptotic confidence interval procedure is supposed to "work" with the stated level of confidence when the sample size is large. However the U.S outbreak was not what is typically considered large with only 8 observed cases and 17 potential cases that could have occurred. Simulation studies are useful to evaluate the performance of a statistical procedure in small sample sizes that theoretically works in large sample sizes. A simulation study revealed that the confidence interval procedure used in the analysis of the anthrax outbreak performed very well even though the sample sizes were small (Brookmeyer and Blades, 2003).

In summary, while models can help fill in critical gaps in knowledge there are important sources of errors including sampling error and model assumptions. A variety of approaches can be used to evaluate and assess uncertainty in the results including confidence intervals, sensitivity analyses and simulation studies. Bayesian methods can also be used to incorporate and tie together many of the sources of uncertainty.

Model Implications

Over ten thousand persons were treated with antibiotics to prevent disease in the fall of 2001 in the anthrax outbreak in the United States. Yet, public health officials did not have any idea if cases of disease were prevented by the public health control measures and if so how many. The case study presented in this chapter illustrates that a statistical model can piece together various sources of data into a coherent picture to answer these critical questions. .

A byproduct of the analysis was an estimate of the date persons in the Florida media publishing company were exposed to the letter contaminated with anthrax spores. If in a future outbreak the date of exposure is unknown, then statistical analyses can estimate the date of exposure and perhaps help identify the perpetrator of an act of bioterrorism or identify other persons who may have also been exposed to the infectious agent and could benefit from medical care.

Several important messages follow from these analyses. Antibiotics halved the numbers of cases of disease indicating that the public health control measures likely saved lives. Yet even without antibiotics, the 2001 U.S outbreak was unlikely to have been greater than 50 cases. Over 10,000 persons were treated with antibiotics to prevent roughly a handful of cases of disease. Because widespread use of antibiotics could result in significant numbers of adverse reactions, an important question raised by our results is whether more targeted and limited distribution of antibiotics to those persons at highest risk could have prevented roughly a similar number of cases of disease while minimizing unnecessary antibiotic use. A related question is how long people really need to stay on the antibiotics to make sure they don't get sick. Models can help answer that question too (Brookmeyer, Johnson and Bollinger, 2003; Wein, Craft, and Kaplan, 2003; Brookmeyer, Johnson and Bollinger, 2003) The anthrax outbreak heightened awareness of the critical importance of rapid detection of outbreaks together with effective and targeted control measures in protecting the health of the public.

Models similar to the kind used in this chapter are also used to track other kinds of epidemics. For example, a method to predict future trends of the HIV/AIDS epidemic called back-calculation (Brookmeyer and Gail, 1994; Brookmeyer, 1991) is based on an idea similar to the iceberg phenomenon. One difference is that HIV infection is transmitted from person to person and so infections can occur continuously in time rather than at a single time point as in a common source outbreak. HIV infection is characterized by a long and variable incubation period with a median of about 10 years. Similar ideas have also been used to model the epidemic of bovine spongiform encephalopathy among cattle in the United Kingdom, also known as mad cow disease and the subsequent epidemic it spawned in humans called variant Creutzfeldt Jakob disease (Donnelly and Ferguson, 2000). .

Questions for Discussion

1. Why is it of public health interest to know how many cases of disease were prevented by the antibiotics program?

2. Suppose the incubation period distribution is $F(t)=1-e^{-.03t}$ where *t* is the number of days since exposure. That is, *F (t)* is the proportion of infected persons that are symptomatic at or before *t* days after exposure to the infectious agent. Now, suppose you have seen a total of 16 cases by the 7th day following exposure. What would be your estimate of the number of people ultimately getting sick in this common source outbreak (answer: about 85)

3. What is the median incubation period for the distribution in question 2?

4. Can the iceberg phenomenon be useful in other kinds of diseases? For example, can it be used with diseases with very long incubation periods? Very short incubation periods? Diseases where the incubation period is very variable? Diseases where there is little variation in the incubation period?

5. If we can detect an outbreak more quickly will we be able to prevent more people from getting sick? If so, under what conditions?

Figure Legends

Figure 1 The iceberg phenomenon. If X cases become symptomatic t days after exposure then $N = X/F(t)$ estimates the total number of cases in the common source outbreak.

Figure 2: Lognormal incubation period probability density of inhalational anthrax (based on the analysis in Brookmeyer, Blades, Hugh-Jones and Henderson (2001)).

Figure 3. Dates of exposure to anthrax spores (symbol *E*), and dates when people began to use antibiotic prophylaxis (symbol *P*) in each of three clusters: workers at the Florida publishing company (circles), postal workers in New Jersey (squares) and postal workers in Washington, D.C. (triangles). Also shown are the dates that cases became symptomatic in each of the three clusters.

Figure 4: The likelihood function for the size of the 2001 U.S. outbreak (*N*) if antibiotics had not been initiated

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Figure 1

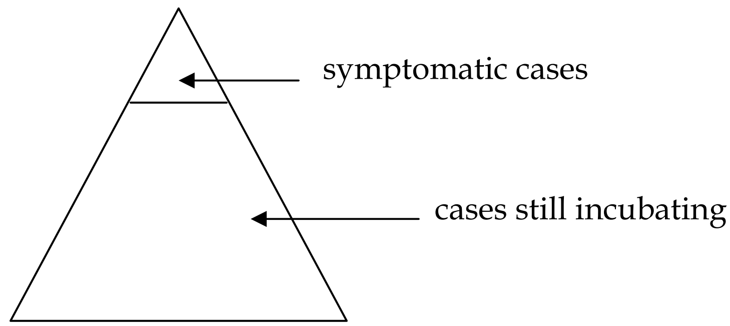


Figure 2

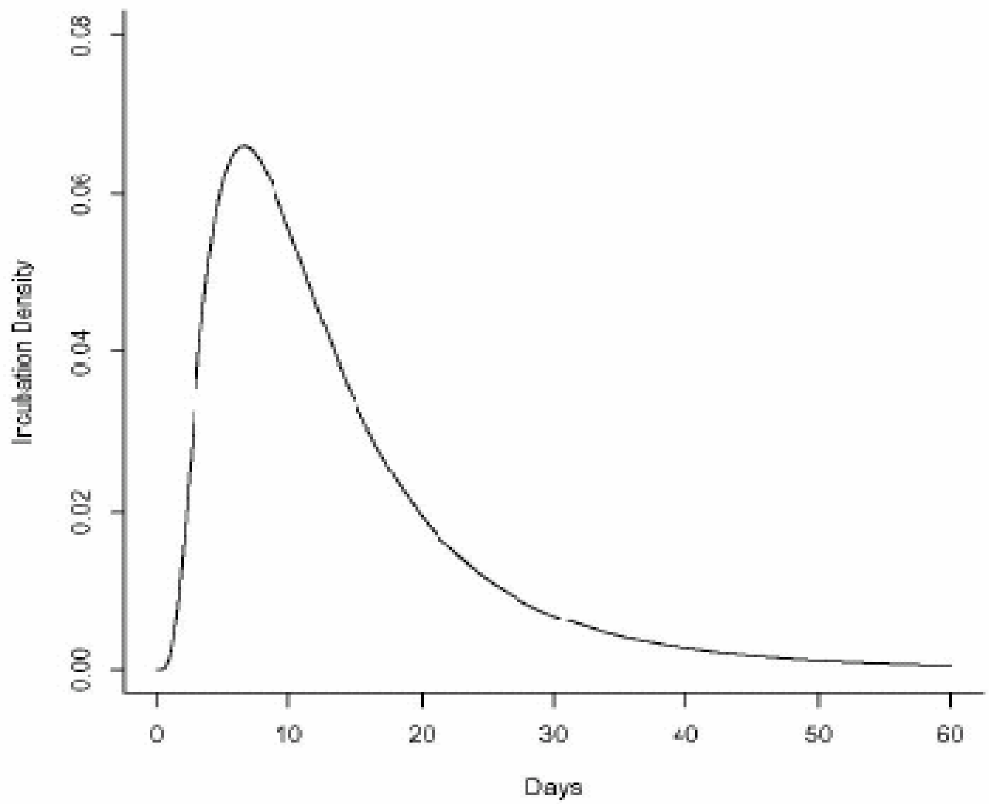
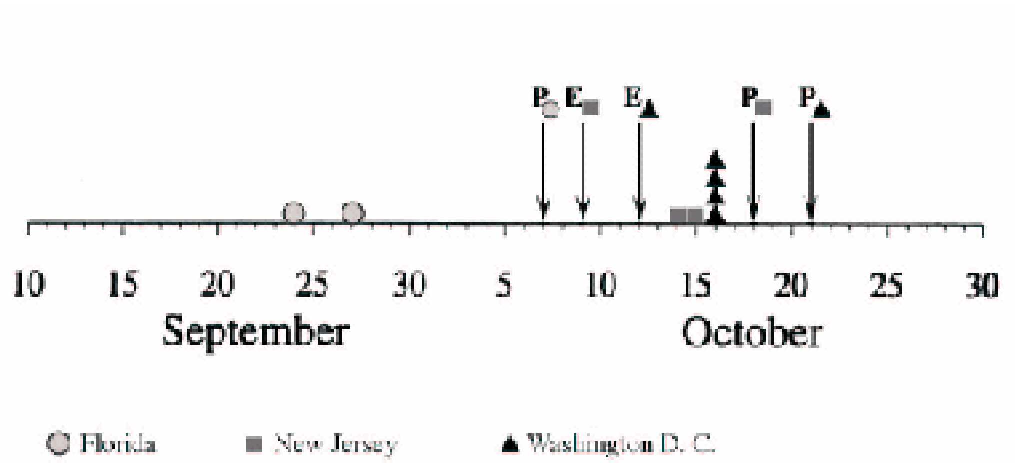


Figure 3



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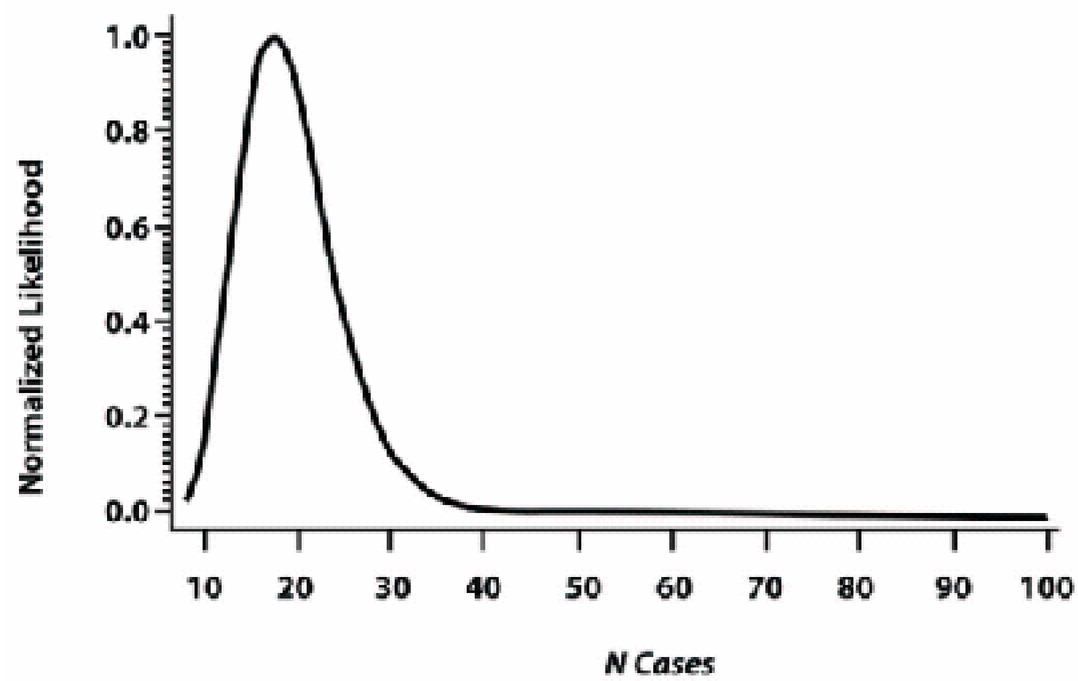
10 15 20 25 30 5 10 15 20 25 30
September
October
Florida
New Jersey
Washington D. C.

Figure 4


Normalized Likelihood
1.0
0.8
0.6
0.4
0.2
0.0
10
20
30
40
50
60
70
80
90
100
N Cases