

Statistics in Defense and National Security: Bioterrorism and Biosurveillance

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In 1334 an epidemic struck the northeastern Chinese province of Hopei. This “Black Death” claimed up to 90% of the population, nearly five million people. The epidemic eventually reached and decimated Tartar forces that had been attacking Kaffa, a Genoese colony on the Crimean Peninsula. In 1347, the departing Tartars catapulted plague-infested bodies into Kaffa. The Genoese quickly dumped these bodies into the sea, however it was too late. Four ships escaped back to Italy carrying the plague that in just two years killed one-third of the European population.

Today we have antibiotics to overcome the plague, however, this early example of bioterrorism stands as a reminder of our vulnerabilities. This point was reiterated after the attacks of September 11, 2001 revealed our vulnerability to terrorism in general. Shortly thereafter, anthrax in letters delivered by the U.S. Postal Service caused five deaths and thirteen confirmed additional infections, bringing the specific threat of bioterrorism into our consciousness. (See Jernigan JA et. al. (2001) for a detailed description of the first 10 cases.) These attacks have motivated an increase in bioterrorism-related research, and this evolving research area is creating new challenges, responsibilities, and opportunities for statisticians.

Bioterrorism refers to the intentional release of organisms that can cause sickness or death. The Centers for Disease Control (CDC) classifies organisms into three categories based on the ease of dissemination or transmission, potential for major public health impact (high mortality), potential for public panic and social disruption, and requirements for public health preparedness. Category A agents (the most dangerous) include anthrax, smallpox, plague, botulism, tularemia, and viral hemorrhagic fever viruses such as Ebola. Research on many of these organisms require “biosafety level 4” (the highest level of containment) facilities. We focus on anthrax; the agent used in the well-publicized recent bioterrorism attacks.

Anthrax

Anthrax is an acute disease caused by the bacterium *Bacillus anthracis*. Human anthrax has three major clinical forms: cutaneous, inhalation, and gastrointestinal. The most dangerous form, inhalation anthrax, is fatal in 90% of untreated cases. Two phases of symptoms are associated with this form. The first phase, with onset typically several days after exposure, has symptoms similar to the common cold or flu. Symptoms, once they appear, are non-specific but usually involve a cough or other respiratory complaints and last two to four days. In the second phase, respiratory distress, severe sweating, and eventually shock occur. If undetected or untreated, then death is likely. However, timely

treatment (antibiotics in the first days of infection) usually results in a complete recovery. Ciprofloxacin (cipro), penicillin, and doxycycline have been approved for treatment. Anthrax can be diagnosed via chest X-ray, but few physicians will obtain a chest X-ray for the non-specific symptoms present in the first phase of illness. Anthrax is not easily transmitted by person-to-person contact.

Public health officials recommended antimicrobial prophylaxis (AP) to people exposed to inhalation anthrax in recent attacks. Brookmeyer and Blades (2002) suggest that the 18 observed cases do not represent all of the cases that would have occurred without use of AP and use statistical models to estimate the number of cases that may have been prevented by AP use. The applied statistical methods require knowledge about the incubation period, and the results are sensitive to assumptions made about this incubation period. The incubation period of anthrax is variable (Brookmeyer et. al., 2001), however, observed cases generally have incubation periods that are shorter than the time interval between exposure and AP use. The authors also had to estimate the date of exposure in many cases. They argue that the epidemic could have been twice as large without a timely AP regimen. These results underscore the importance of an effective surveillance program.

Biosurveillance

We define biosurveillance as the attempt to detect bioterrorism. The primary objective of biosurveillance is to minimize the time between exposure to the biological agent and public knowledge of exposure. Recognition of a bioterrorist attack and rapid identification of exposed persons is paramount in minimizing mortality and morbidity among those already exposed and in preventing the exposure of additional people to the agent.

Ideally, surveillance will detect a large- or medium-scale dissemination of anthrax before any victims enter the second phase of the illness. Due to the non-specificity of the symptoms in the initial phase, surveillance based only on confirmed cases is unlikely to meet this goal. It is unlikely that anthrax will be suspected in this time frame (let alone diagnosed) even for the cases with the earliest onset of symptoms. Small-scale attacks are likely to go undetected until second-phase symptoms are present in some victims. Therefore, in the first phase, surveillance must be based on alternative methods.

The Boston Public Health Commission has a very simple monitoring system. Every evening, city hospitals submit the number of emergency room cases to a central computer. If an unusually high volume of cases is detected then an explanation is sought, potentially revealing an emerging disease cluster. However, an “unusually high volume of cases” is not well defined and better statistical mechanisms for identification are needed.

A group of researchers at Children’s Hospital in Boston and at the Harvard School of Public Health are working on another surveillance system. Emergency department data from several hospitals are linked together via a central computer. The system observes in

real time the number of patients arriving for treatment at the emergency rooms. The system notes the number of patients reporting to the hospitals, the syndromes associated with their complaints, and the patients' addresses. A geo-temporal analysis can compare these data with historical records to determine if a stable system is experiencing a disturbance, in which case an alarm needs to be raised.

In a broader area of eastern Massachusetts, a collaborative group consisting of a health care provider group (Harvard Vanguard Medical Associates, HVMA), an HMO, an academic department, and the state Department of Public Health has designed and implemented another surveillance system that is based only on the non-specific symptoms that characterize the initial phase of inhalation anthrax. Patients whose primary care providers belong to the health care provider group and are insured by the HMO are part of the system. These patients comprise about 10% of the population in the Boston region.

One approach to using these data for biosurveillance uses time-series analyses, or other monitoring of overall counts. This approach has been adapted for surveillance purposes in several recent papers (e.g. Farrington et al. (1996), Williamson and Hudson (1999), Stern and Lightfoot (1999)). Another approach makes use of spatial statistics to test for clustering (Kulldorf, 2001).

Yet another approach uses a generalized linear mixed model, treating the census tracts as individuals. Using historical data, the model estimates month, day of the week, holiday, and secular time fixed effects, in addition to a random effect for each census tract. These estimated random effects (also known as shrinkage or empirical Bayes estimators) can be used to get a different parameter estimate for each tract on each day, which may then be compared to observed counts.

The statistician will recognize the typical hypothesis-testing problem in biosurveillance. We run the risk of raising a false alarm (Type I error) or not raising an alarm that needs to be raised (Type II error). Since the system is evaluated daily, use of a naïve type I error rate of 5%, would translate into more than one false alarm a month on average. As a result, alarms generated by the system may become so common that they would not be taken seriously and ignored like car alarms. Parenthetically, within the first few weeks of the anthrax outbreaks, the Massachusetts Department of Public Health Laboratory processed over 1000 substances feared to be Anthrax (all were negative). On the other hand, failing to identify a true attack could be disastrous.

These projects reflect passive surveillance in which data that has been collected for other purposes is now being used for surveillance. Active surveillance, where one is collecting data for the sole purpose of surveillance (e.g., the use of cameras and microphones at key assembly locations such as commuter stations at rush hour or lobbies of large office buildings, to observe coughing or other behaviors), presents novel statistical sampling problems. These systems also result in a loss of privacy. How do we obtain this valuable information yet maintain privacy rights?

Sophisticated DNA detectors that continuously monitor the air for particular pathogens are also being developed for surveillance. Such detectors identified trace amounts of anthrax recently at the Pentagon. Surveillance methods can further extend to linking purchasers of biological or other materials to their activities (Goldenberg et. al., 2002). In addition, Washington D.C. postal facilities are scheduled to use electron beam units that sanitize mail beginning in November.

Clinical Trials

Clinical trials are often used to develop and evaluate treatments and vaccines for biological agents. However in the context of bioterrorism, it is difficult to conduct human trials since it is unethical to administer dangerous agents to humans and known cases of disease are infrequent in nature. A trial in monkeys forms the basis of our knowledge of treatments for anthrax. Forty monkeys were made to inhale anthrax for one day. Ten monkeys were assigned to each of four treatment groups (cipro, penicillin, doxycycline, and placebo). They were then treated for 30 days, after which treatment stopped and they were observed for 30 additional days. Nine of the ten monkeys in the placebo group died within the first 30 days of “treatment”, and the final monkey survived the next 30 days as well. None of the ten monkeys treated with penicillin died over the treatment period, but three died over the subsequent 30 days. No monkeys in the cipro or doxycycline arms died during the treatment period, however, one monkey in each of the two treatment arms died over the subsequent 30 days.

Vaccine research is another approach to addressing bioterrorism. Anthrax vaccine adsorbed (AVA) is the only licensed anthrax vaccine. However, the long schedule for administering AVA makes it impractical for use in a bioterrorism incident. The regimen also differs for various populations.

Don Rubin of Harvard University is working on two anthrax vaccine trials sponsored by the CDC, one on humans and the other on rhesus monkeys. Rubin notes the very interesting and challenging statistical aspects of this research including issues with bridging studies, surrogate endpoints, and missing data. The human trial has six treatment arms (five active and one placebo) and is designed to determine the best delivery system for the vaccine, what dose level is safe, and how long the vaccination lasts. Since one cannot ethically infect humans with anthrax, the trial uses biomarkers or surrogates for disease. The trial is also long and has numerous missing data issues. The monkey trial has similar treatment arms to the human trial and although the monkeys are substantially different in weight (relative to humans), the monkeys are administered the same doses as the humans. However the monkeys are infected with anthrax and thus may perish from the disease. The two “bridging” studies (the human and the monkey trials) are then interpreted simultaneously to address the objectives of the trial by the use of surrogate endpoints.

However, vaccines have several limitations. Vaccines are disease-specific and there are more weapons in a bioterrorist’s arsenal than there are vaccines. There is no guarantee that a vaccine can be developed for a given agent. Even if one can be developed, vaccine

development can take a long time. Also, vaccines themselves are often not very safe. A conservative estimate is that one in one million people that are administered the smallpox vaccine would die from the vaccine. (There would also be considerable morbidity.) Strategizing vaccine deployment presents a problem of statistical morality. Without any vaccine, many die. With a vaccine, fewer die. However, there is no guarantee that those who die under vaccination would have died under the choice of no vaccination. We, as a society, usually choose to vaccinate, as is evident by all the vaccines to which we subject our children. However, in 1974, vaccination against smallpox ceased, even before the disease had been eradicated, and a containment strategy was implemented. Strategies other than total vaccination can be entertained. Statisticians should play a role in these decisions.

Government Funding

Federal spending for bioterrorism defense increased from an original 2002 budget of 1.5 billion to five billion dollars after September 11, 2001. The proposed budget for 2003 is six billion dollars. The government has several research programs to address these issues.

Dr. Anna Johnson-Winager, a Deputy Assistant Secretary of Defense, noted that the Department of Defense (DOD) has a one billion dollar budget to conduct chemical and biological defense research through the Chemical-Biological Defense Programs, consisting of five research areas: (1) detection and warning systems such as automated sensors that sample air from the environment, (2) medical research relating to drugs and vaccines for prevention or treatment, (3) individual protection items such as gas masks and clothing, (4) decontamination research often conducted with the EPA concerning the clean-up of contaminated sites, and (5) modeling and simulation research used for decision making purposes based on dispersion predictions, casualty estimation, and other analyses.

Statisticians are frequently consulted to help design studies and answer research questions in these areas. For example, consider building a detection system using automated sensors. How many samples (and detectors) are needed to have high power to detect a pathogen? And where should these sensors be located to obtain the most efficient surveillance? Consider evaluating the effectiveness of a decontamination effort. How many “negative” samples are needed to conclude that the clean up is complete?

The National Institute of Allergy and Infectious Diseases (NIAID) is the primary National Institutes of Health (NIH) branch that supports and conducts research on the diagnosis, prevention, and treatment of infections caused by bioterrorist agents. NIAID has developed a Strategic Plan for Counter-Bioterrorism Research and a Counter-Bioterrorism Research Agenda focusing on the need for research on: the biology of the microbes, the host response, diagnostics, therapeutics, vaccines, and research resources. Statisticians need to play an integral role in these research areas.

Statistical Challenges and Unanswered Questions

Prior to the recent intentional dissemination of anthrax, only 18 cases of inhalation anthrax were reported in the United States in the past century. With such sparse data and limited experience, statistical (and medical) challenges are immense. How can we draw conclusions with such a limited number of cases? How can we evaluate biosurveillance methods (i.e., perform power calculations) if we do not know the dynamics of a large attack and thus how to simulate such an attack? How many anthrax cases have been missed in the past? What is the relationship between the quantity of exposure and risk of disease (dose-response)?

Other organisms present additional challenges. Some diseases are viewed as even more dangerous than anthrax as some of these agents are more easily spread by person-to-person contact (e.g., smallpox) and have no known curative treatment (e.g., most viral infections). Furthermore, some diseases can be spread by contamination of our food supply (e.g., mad cow disease).

The potential impact of statisticians in the war on terrorism (and bioterrorism) is immense. Statistical expertise is paramount to effective bioterrorism research. Indeed, the world is asking for our help.

Committee for Statisticians in Defense and National Security

The ASAs' Committee for Statisticians in Defense and National Security (DNS), recognizing the importance of communication, is creating a network of statisticians that currently work on (or have an interest in) statistical issues in DNS. Ultimately, a directory of statisticians with varying areas of expertise will be available to discuss and consult on DNS issues. The Committee encourages interested statisticians to visit the Committee's ASA website or the Committee's independent website <http://www.statdns.org/> and submit contact information for future communication.

The Committee is sponsoring an invited panel session at JSM entitled "What Can Statisticians Do to Contribute to the War on Terrorism". The panel will discuss several areas in which statisticians can apply their skills including (1) the use of biostatistics to fight bioterrorism, (2) changes in the testing of weapons systems to speed new capabilities to troops, (3) techniques for providing information integration and critical infrastructure protection, and (4) use of statistical modeling to predict effects on urban areas of weapons of mass destruction. Risks of terrorism will also be discussed and a Q&A session will conclude the session. The Committee is also sponsoring a Mixer at JSM (please look for details to be provided in the next edition of AMSTAT News). Interested statisticians are invited to attend.

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