

Challenges to Rapid Clinical Detection of Select Agents

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Oftentimes a debate is joined between those who advocate either clinical detection or syndromic surveillance as faster and more reliable than the other approach. This is really a false debate, since clinical detection and syndromic surveillance both work best when they are working together as a team. Syndromic surveillance can be used to cue clinicians to be on the lookout for certain types of rare diseases that they would not normally include in their differential diagnosis. On the other hand, only clinicians can confirm the suspicions raised by syndromic surveillance with more specific tests.

Early symptoms of select agents are very similar to those of flu-like illness. This means there is often a high background rate of such symptoms in a population. A good syndromic surveillance system may be able to detect an outbreak when the numbers of such syndromes increase by say, 30% over the prevailing rate. So if there are routinely 100 cases of flu-like illness in a metro area, there would have to be 130 presentations of such syndromes recorded in order to trigger an alert statistically. Some providers believe that they could easily discern if there were a 30% increase in such clinical presentations. However, averaged out across a number of clinics, and over a number of days, those 30 cases could easily be lost "in the noise" of the routine business of clinical providers. In addition, a number of providers across several clinics would need to notice such an increase in cases in order for there to be an indication that a significant broader community-wide event was taking place. Syndromic surveillance can accomplish such

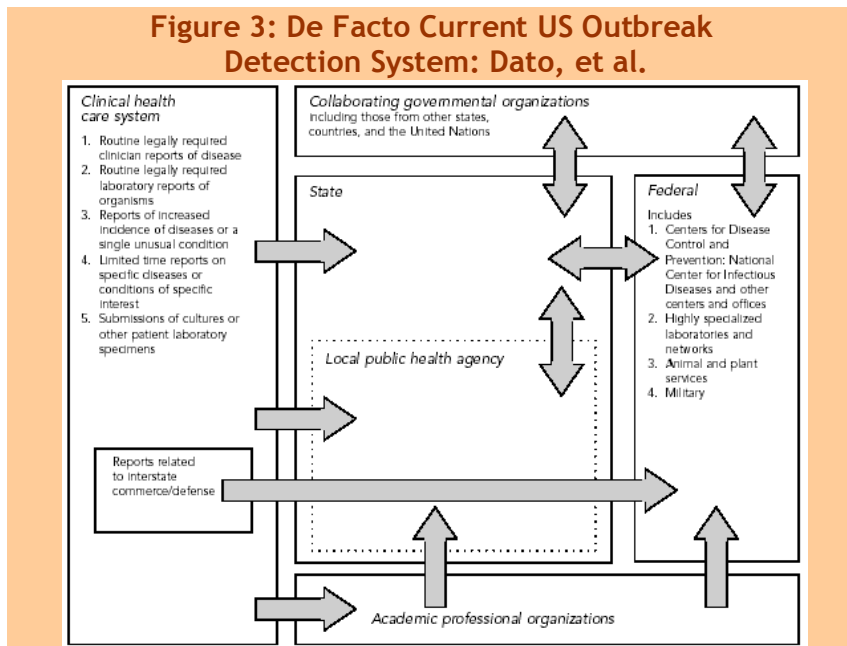
routine data monitoring and statistical alerting. It doesn't sleep, it "does the math," and it doesn't get bored. After all, it's just a tool for the local Public Health professional.

As for providers alone, there are a number of challenges to clinical detection of select agents. Many physicians are not even very thoroughly trained at medical school in infectious disease or Public Health (Zelicoff, 2005). In the not too distant past, before the emergence of AIDS, much medical opinion considered that the overall danger of infectious disease was diminishing. Less emphasis was placed upon it in medical school than other specialties. Indeed, it was the unusual occurrence of opportunistic infections that helped epidemiologists to determine that the AIDS outbreak was taking place. It is sometimes in the HIV context that physician interest in infectious disease has revived. However, very few physicians have seen actual cases caused by Category A pathogens, and the cohort that may have seen smallpox (the notable exception) in the past are aging and leaving practice.

The physician and Public Health communities are also, somewhat surprisingly, separated. Generally, physicians treat an individual's illness, while Public Health seeks to prevent disease in a population. Zelicoff claims the distance is exacerbated because physicians are not comfortable with the discipline of statistics, while epidemiologists may not be physicians. In practice, the person most involved in detecting local outbreaks on a daily basis is the Infection Control Practitioner (ICP) in local hospitals. ICPs may be nurses fulfilling a staff function, especially identifying nosocomial outbreaks and limiting their spread (vice looking for Category A-type diseases). Local Public Health may create relationships with ICPs, and the better those relationships, the more likely and sooner it is

that they will hear about local outbreaks in hospitals, especially if such outbreaks are not of officially reportable diseases. Obviously, such diseases must also be officially diagnosed, usually by laboratory tests, before they are confirmed cases. That process takes far too long to be useful in stemming a bioterrorism attack.

Outbreak cases like the Cryptosporidium in Milwaukee or even the initial HIV/AIDS detection indicate the complexity and somewhat haphazard nature of current de facto outbreak detection methods. Not surprisingly, most outbreaks are now recognized retrospectively, after they have run their course. The process needs to be streamlined or superseded altogether in order for outbreaks can be detected while there is still time to significantly mitigate their effects (Dato, Wagner, and Fabohunda, 2004). The figure below describes the current practice of outbreak detection in the US.



In 2001 University of Pittsburgh researchers reviewed the last two years of CDC's Morbidity and Mortality Weekly Reports to identify outbreaks detected, and the methods used (Dato, et al. 2001). They found 66 detection systems supporting clinical health care systems; local, state and federal government organizations; and academic professional organizations. They found 51 outbreaks reported in the literature. Of these 53% were detected from Health Department staff as the result of aggregating reports. 28% were reported as suspected outbreaks to the Health Departments, but only three of these by "astute clinicians." Of the detections whose timeliness could be measured in the data, 42% were detected in one week; 29% between one week and one month after initial case, and 29% after a month or more. This approach to outbreak detection was not as effective as one might wish or expect at the beginning of the 21st century in America.

In a different study, Ashford et al. reviewed 1,099 outbreak investigations by the CDC's Epidemic Intelligence Service from 1988 to 1999 (Ashford, et al., 2003), including 44 outbreaks caused by potential bioterrorist agents. 36% of all the outbreaks were first recognized by healthcare providers or ICPs., while 31% were recognized later by Health Departments. The time delay from first case to recognition ranged from 0-26 days.

In addition, some number of outbreaks go undetected. Dato et al. found multiple reports of outbreaks that involved contamination of nationally distributed products. However, the health departments of only one or two states recognized these outbreaks, suggesting that outbreaks in other states went undetected. As reported by Wagner and colleagues, these outbreaks involved contaminated processed deli meat, burritos, orange juice, parsley and dip (Wagner, et al., 2005, p.16). Another example is the contaminated ice

cream that was delivered to a number of states, but the salmonella resulting from its ingestion was reported in far fewer (Hennesy et al, 1998). Even if a disease is detected that is legally required to be reported, studies show less than 10% of such cases are actually reported to authorities as they should be (American Journal of Epidemiology vol. 155(no. 9), May 2002, pp 866-874).

Reporting may take a comparatively long time for physicians or be cumbersome to perform. It may also be potentially embarrassing for the patient. Also, the physician may not be aware that the disease is required to be reported. Systems that rely on human intervention and input for case reporting have a troublesome compliance rate, including some early syndromic surveillance systems. Questionable compliance puts at risk any sort of subsequent statistical analysis of those data.

Physician recognition of diseases produced by Category A and B pathogens can be challenging. Doctors have likely never seen cases of the diseases previously. (Because many of the pathogens of interest are zoonoses, veterinarians may have seen animal cases). In the famous aphorism, medical students are told that when they hear hoofbeats, think horses, not zebras. The point being made is that if they see influenza-like symptoms presented, they should presumptively treat patients as though they had the most common cause of such symptoms, rather than more obscure ones such as Category A pathogens.

A study of 631 physicians from 16 states correctly diagnosed anthrax, smallpox, pneumonic plague, and botulism less than half the time, and they made correct management decisions only a quarter of the time, according to a recent report in *Archives of Internal Medicine* (Cosgrove et al, 2005).

Even if clinicians suspect such rare pathogens, many such diseases have diffuse symptoms that lack specificity and are hard to recognize. For instance, four Amerithrax anthrax victims were sent home with three different diagnoses (Buehler et al, 2004). For the Sverdlovsk anthrax outbreak in 1979, the diagnosis was made ten days after the accidental release at autopsy of one of the victims who had hemorrhagic meningitis (Guillemin, 1999, p. 51). 21 victims had died before the diagnosis was announced, about one third of the total there would be.

Brucellosis, another disease of concern, has an incubation period in humans that varies from five days to several months. Disease onset may be abrupt or insidious, with symptoms varying, especially in the early stages. Even experienced physicians in countries where brucella is indigenous in the milk supply may be challenged to diagnose brucellosis because the presentation is so nonspecific, and tests are lacking.

Another example of a disease that is hard to diagnose is the typhoidal form of Tularemia (one of the two ways, along with pneumonic, that *F. tularensis* is expected to present in the event of an aerosol terrorist attack). Typhoidal tularemia presents with fever without visible foci on skin and without lymphadenopathy. An example of how challenging diagnosing tularemia can be is seen in a recent outbreak in Boston. Three workers at a

Boston University (BU) laboratory were inadvertently exposed to *F. tularensis* in BU's current high containment facility. Clinicians did not suspect tularemia until several days after the second patient's hospital admission. Specific tests to detect tularemia were not ordered until September. The test results came back positive only on 29 October. Public Health authorities were not notified of Tularemia, a reportable disease, until 9 November 2004. (The patients recovered and the BU Principal Investigator was replaced) (Shane, 2005).

Other examples of laboratory-acquired infections post 9/11/01 that are mis- and non-diagnosed include an additional case of anthrax (MMWR, 2002), several cases of brucellosis and one of glanders. A convenience sample of laboratory acquired infections for Select Agents revealed that all noted were not readily diagnosed. The anthrax case was a cutaneous one that took place in Texas with a laboratory worker. Lack of recognition led to systemic bacteremia risk for the patient. We shall summarize several other cases at greater length to illustrate the nefarious nature of some of the diseases caused by select agents, as well as some surprising difficulty in detecting them clinically. One brucellosis case took place in a 57-year-old female laboratory worker who began experiencing nonspecific symptoms of malaise, vomiting, headache, lower leg cramping, anorexia, and fever (Noviello et al, 2004). One week after symptoms, she was evaluated for severe headaches at a local Emergency Department (ED), where cerebrospinal fluid (CSF) and blood cultures were collected. The CSF culture was negative. From the blood culture, small, gram-positive bacilli were isolated & characterized as coryneform bacilli, which are usually interpreted as contaminants of unknown clinical importance. Despite

multiple hospital admissions, the laboratory worker continued to have symptoms, but her condition remained undiagnosed. Approximately 5 weeks after symptom onset, colleagues from the hospital microbiology laboratory where she was employed drew her blood for culture again. After 5 days of incubation, gram-variable coccobacilli, later identified as *Brucella* spp., were isolated. The laboratory worker was treated with doxycycline and gentamicin, followed by doxycycline and rifampin, for 6 weeks of outpatient therapy. The isolate was later identified as *B. melitensis* by the Wadsworth Center and confirmed by the Centers for Disease Control and Prevention. The patient had not relapsed 18 months after completing treatment.

Noviello and colleagues also describes the case of a 48-year-old woman who had nocturnal temperature spikes to 40°C, chills, drenching sweats, and weight loss. Initially she was diagnosed with influenza and treated with oseltamivir. Symptoms persisted, and uveitis (an inflammation of the interior of the eye) developed. In early March 2002, a diffuse rash appeared on the anterior aspect of both her legs. The patient received a blood culture and serologic tests for Lyme disease, ehrlichiosis (any of several diseases caused by rickettsia of the genus *Ehrlichia* transmitted by ticks), and Rocky Mountain spotted fever (RMSF). Gram-positive cocci from the blood culture were isolated and identified as *Micrococcus* spp. by a commercial laboratory. Her physician prescribed 3 weeks of doxycycline for RMSF, and the fevers resolved. Subsequently, she was referred to an infectious disease specialist, who found repeat RMSF titers unchanged, which made acute RMSF unlikely. Additional testing identified possible *Brucella*. When interviewed by New York State Department of Health staff, the patient reported that she was a

laboratory worker at the same laboratory as the previous Brucellosis case discussed here. Her initial blood culture specimen, which had originally been identified as *Micrococcus*, was reassessed by the commercial laboratory. The commercial laboratory referred the original isolate to the Wadsworth Center, where the isolate was identified as *B. melitensis*. Both these laboratory workers had previously analyzed samples from a patient known to have brucellosis.

Another case was described in the June 2000 issue of Morbidity and Mortality Weekly Report (MMWR, 2000). A local health department was notified by hospital staff of a serious systemic febrile illness in a US Army Medical Research Institute for Infectious Diseases (USAMRIID) microbiologist who worked with several pathogenic bacteria, including *Burkholderia mallei*, the causative agent of glanders. The microbiologist, who has diabetes, was well until early March 2000, when he developed an increasingly painful mass in his left axilla (armpit). On March 16, he had a temperature of 101.5 F (38.6 C) and was seen by a primary-care provider. He was given one dose of ceftriaxone intramuscularly and was started on a 10-day course of cephalexin. Despite completing the therapy, episodes of fever increased, and he experienced marked fatigue, malaise, night sweats, and weight loss. A medical evaluation, which included blood & urine cultures and chest x-rays, was unrevealing. In early April, the patient had a 10-day course of clarithromycin and improved; however, 4 days later his symptoms returned. He continued to lose weight and experienced mid-epigastric abdominal pain. Multiple blood cultures were negative for bacteria. An abdominal CT revealed multiple hepatic and splenic lesions. Because of increased abdominal pain, hyperglycemia, and diabetic

ketoacidosis (acidosis caused by the increased production of ketone bodies, as in diabetic acidosis), the patient was admitted to hospital. Because of the patient's work history, *Burkholderia* infection was considered, and one dose of piperacillin-tazobactam was administered intravenously. On the second hospital day, the patient developed respiratory distress requiring mechanical ventilatory support. He was placed in respiratory isolation, given intravenous tobramycin and doxycycline, and transferred to a second hospital for further treatment. May 4, the initial hospital identified small, bipolar, weakly-staining Gram-negative rods in cultures of the liver abscess fluid. On May 5, Gram-negative bacteria also were isolated from the blood cultures. An automated bacterial detection system at the initial hospital initially identified the bacteria as *Pseudomonas fluorescens/putida*. However, subsequent studies of the same isolate performed at hospital B and CDC, including motility studies, cellular fatty acid analyses, and 16S ribosome sequencing, identified the organism isolated from the liver abscess as *B. mallei*. This was the first human case of glanders in the United States since 1945. Because the patient worked with strains of *B. mallei* sensitive to imipenem and doxycycline, he was treated with those and he rapidly improved. Repeat abdominal CT obtained after 10 days of therapy showed slight regression of the hepatic and splenic abscesses. The patient was treated with intravenous imipenem and doxycycline therapy for 2 weeks. He was switched to oral doxycycline and azithromycin, and the patient's liver and spleen abscesses continued to resolve.

The above recent examples of laboratory-acquired infections show that even at fine hospitals in a post-9/11 environment, patients with plausible exposure histories

presenting symptoms of Category A pathogens are not necessarily recognized by clinicians. They also show the need (and the challenge!) to develop proliferable tests that could support rapid diagnosis of a Category A pathogens, especially if one particular disease was not suspected. Given a strong enough signal, syndromic surveillance could provide a cue that a possible emergency situation had arisen even in the absence of a confirmed diagnosis. Physicians might consider that as one factor as they decide how to presumptively treat a patient with an unknown but serious illness.

In addition to the difficulties with the particular diagnoses mentioned above, timely clinical detection is not assured for any of the Category A pathogens identified by CDC as high potential threats (Buehler et al, 2004). Most pathogens require specific tests that are neither likely to be on hand nor routinely ordered. The best case, anthrax, may come back positive from a routine test in 18 hours, which still stresses the needed attack response timelines. However, cued clinicians with an increased index of suspicion can do much better at diagnoses, including relatively rapid diagnostic means for anthrax (e.g., Computer Assisted Tomography scans, Cerebro-spinal Fluid gram stains, etc).

Table 2. Multiple Screening Rapidly Becomes Unsustainably Expensive

Table 2a and 2b. Multiple Screening Rapidly Becomes Unsustainably Expensive

No. of symptoms	No. of patients screened	Percentage of patients screened (95% CI) (n = 1127)	Associated charges, US\$
≥6	4	0.4 (0.1–0.9)	1,699.96
≥5	29	2.6 (1.7–3.7)	8,924.79
≥4	71	6.3 (4.9–7.9)	30,174.29
≥3	240	21.3 (18.9–23.8)	101,997.60
≥2	681	60.4 (57.4–63.3)	289,418.19
≥1	1047	92.9 (91.3–94.3)	444,964.53

NOTE. Each patient screened was assumed to receive 1 complete blood cell count, 1 posterior-anterior and lateral chest radiograph, 1 set of blood cultures, and a 10-day course of generic doxycycline (100 mg b.i.d.).

- Data on cost of hospital testing for Amerithrax victims indicates broad routine (uncued) screening may be unaffordable to localities

Screening guideline	Identified patients with IA	No. of patients screened	Percentage of patients screened (95% CI)	Associated charges, US\$
Inova Fairfax protocol [1]	Yes	4	0.4 (0.1–0.9)	1900
Cornell protocol [2]	Yes	273	24 (21.7–26.9)	126,025
Presence of ≥3 clinical symptoms	Yes	240	21.3 (18.9–23.8)	102,000
Possible occupational and/or environmental exposure	Yes	250	22 (20–25)	106,250

The Tables show that during the Amerithrax outbreak, clinicians ordered many more tests for patients presenting one or more symptoms consistent with respiratory anthrax. This cost is unaffordable in the absence of heightened clinical suspicion. In an integrated detection system, syndromic surveillance might focus diagnostic tests to be performed at locations where there is a higher probability of attack, and encourage them to be ordered earlier (Howell et al, 2003).

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