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Primary care Physicians and Bioterrorism : Strategies for Improving Historical Understanding, Clinical Abilities, and Integration with the Public Health Structures in the Context of Bioterrorism

Kenneth Richard Spaeth

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PRIMARY CARE PHYSICIANS AND BIOTERRORISM:

STRATEGIES FOR IMPROVING HISTORICAL UNDERSTANDING, CLINICAL ABILITIES, AND INTEGRATION WITH THE PUBLIC HEALTH STRUCTURES IN THE CONTEXT OF BIOTERRORISM.

Kenneth Richard Spaeth
B.A, Rutgers College, 1991

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Public Health at the University of Connecticut, 2003
PRIMARY CARE PHYSICIANS AND BIOTERRORISM:

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Presented by

Kenneth Richard Spaeth, B.A,
Acknowledgments

I would like to thank Drs. Hansen and Kerins for the time, help, and encouragement they offered me since well before this thesis. I would also like to thank Dr. Grey whose support and guidance has been so valuable these years and especially when it reached halfway around the world.

-KRS
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“Those who oppose the United States will increasingly rely on unconventional strategies and tactics to offset U.S. superiority such as biological or chemical weapons.”

--Defense Secretary William Cohen.

“A bioterrorist attack is likely to be covert - we will know we have been attacked only when people begin to get sick and seek medical attention. In our judgment, it is far more likely that we will realize a bioterrorist attack has occurred when doctors and nurses diagnose the first victims of such an attack.”

--The Center for Civilian Biodefense Strategies

“Physicians today need to be ready to recognize and respond to unusual symptoms that might signal a bioterror attack. Primary care doctors might be the first to spot the danger signs, and their knowledge and rapid action could be crucial for the nation.”

--Tommy G. Thompson
Secretary, Department of Health and Human Services. September 2002

Introduction

In 1992, Francis Fukuyama, then Deputy Director of Policy Planning for the State Department, declared that the fall of the Soviet Empire was the final event marking the victory of western liberal democracy. The world, he argued, had fully and finally been delivered to the unabashed victory of economic and political liberalism. The title of his book on the subject summed up this view: The End of History.¹ At the time, it seemed a possibility: Our enemies had been defeated and the new world order was at hand. Some ten years later, or more accurately, until September 10th, 2001 such a perspective seemed worthy of consideration. The events of September 11th, of course, make such a notion seem woefully naïve.

Instead, a new world enemy been ordained, and it is a different type of enemy: different skin, different culture, different means. This enemy is unfamiliar, elusive, without institutions or uniforms or clear structure, and it wages its violence in
unconventional ways; among these are thought to be weapons of mass destruction of which biological agents are but one means. Many governments, including that of the United States, are taking the threat of such weapons quite seriously, but it is only recently that the American public felt as concerned: the existence and threat of biological weapons became etched into the public consciousness beginning with the index case of the post-September 11th anthrax attacks in October, 2001 and became injected indelibly into it with the first administrations of smallpox vaccine that began, as fate would have it, with four physicians at the University of Connecticut Health Center, Farmington, Connecticut in January of 2003.2

While countless experts describe countless scenarios of how a bioterrorism attack might unfold, one aspect remains constant through all: once an outbreak is identified, the focus is on managing the emergency response. On one level, it is indeed a sensible place to focus. An outbreak from such an attack could become quite large and cause great panic. On another level, such a focus is shortsighted and possibly dangerous.

An evaluation of the presenting signs and symptoms of nearly all the viable biological agents shows that they are highly non-specific, creating a ‘flu-like’ illness in the early stages. As a result, it seems quite likely that after an attack the first cases would be seen in an outpatient setting, when such patients seek out a primary care. Yet, a survey of the burgeoning body of bioterrorism literature indicates a failure to address this likelihood. Medline searches reveal virtually nothing directed at responding to or managing biological agents in the outpatient setting. This oversight is further reflected in the emergency response emphasis seen at the federal and state levels, where, with the exception of the CDC, little is offered in the way of training, preparing, or generally
involving primary care physicians in the management of an outbreak from biological agents. Such lack of attention has resulted in a troubling outcome: both formal and informal surveys indicate that outpatient clinicians are terribly unprepared to respond to infections with or to the issues of biological weapons.

**Objectives**

A tremendous void exists, then, in regards to educating, training, and helping those working in the outpatient setting. This paper endeavors to begin to fill the void by addressing the following areas relating to bioterrorism and primary care:

- Providing a historical and geopolitical context of the development and threat of biological weapons
- Addressing patient questions/concerns/education regarding biological agents
- Addressing physician questions/concerns/education regarding biological agents
- Diagnosing infections from biological agents
- Management-prior to, during, and following infection with biological agents.
- Keeping contacts, staff and self, safe from secondary infection
- Engaging and interacting with the public health infrastructure in the event of an outbreak

The purpose of this paper is to begin to address such voids; thereby, creating a resource for physicians in the outpatient setting that is comprehensive, practical, and easy to use. Ultimately, the hope is to formally publish the document in some form and have it made available to physicians for use in the clinical setting with the goal of better equipping physicians for the challenges of bioterrorism from a patient, medical, and public health perspective.

By making primary care physicians better able to identify, manage, and involved in bioterrorism, any bioweapons emergency will more likely be identified sooner, which, in turn, would result in an outbreak that is less severe, contained faster, and involve fewer victims.
Materials and Methods

In making the determination that the resources available to the physicians in the outpatient setting were inadequate, a number of measures were employed.

An in-depth review of the literature was done on Medline, that included searching on key words of “bioterrorism” and “biological agents” with such words as “primary care,” “outpatient” and “preventive.” Additionally, Medline was searched for articles with keywords of simply “bioterrorism” and “biological agents” as well as for specific biological agents.

Additional sources used included the website for the Center for Disease Control and Prevention (CDC) which has extensive information relating to bioterrorism. Similarly, governmental websites such as those of the US Army Medical Research Institute of Infectious Diseases (USAMRIID), Homeland Security, The Federal Bureau of Investigation (FBI), the Department of Health and Human Services (DHHS), etc. Additionally, countless non-governmental websites were searched, such as the Center for Civilian Biodefense Strategies (CCBD), American College of Physicians, various hospitals and universities, etc.

Textbooks for both infectious disease and bioterrorism were utilized, as well.

In addition, informal conversations took place with numerous physicians working in the outpatient setting as means of attaining thoughts and insights about issues relating to biological agents. Similarly, informal conversations occurred with staff at the Connecticut State Department of Health as well as with staff members at the CDC in an
effort to gain insight into the perspectives of the public health infrastructure at the state and federal levels regarding bioterrorism and clinician preparedness.

**Classification of the Agents**

Though the array of potential sources of biological agents is vast, this paper will focus on the most likely and the hazardous agents: Category A.

The Center for Disease Control and Prevention (CDC) has assessed agents it deems as potentially viable weapons (see Table 1). The Agency warns that “The U.S. public health system and primary healthcare providers must be prepared to address various biological agents, including pathogens that are rarely seen in the United States” and has categorized these agents as A, B, and C defined as follows:

### Table 1

<table>
<thead>
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<th><strong>Category A Diseases/Agents:</strong> High-priority agents. These include organisms that pose a risk to national security because they:</th>
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<tbody>
<tr>
<td>• Are easily disseminated or transmitted from person to person</td>
</tr>
<tr>
<td>• Result in high mortality rates and have the potential for major public health impact</td>
</tr>
<tr>
<td>• Might cause public panic and social disruption</td>
</tr>
<tr>
<td>• Require special action for public health preparedness</td>
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<tr>
<th><strong>Category B Diseases/Agents:</strong> Second highest priority. These including organisms that:</th>
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<tr>
<td>• Are moderately easy to disseminate</td>
</tr>
<tr>
<td>• Result in moderate morbidity rates and low mortality rates</td>
</tr>
<tr>
<td>• Require specific enhancements of CDC's diagnostic capacity and enhanced disease surveillance.</td>
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<th><strong>Category C Diseases/Agents:</strong> Third highest priority agents. These include emerging pathogens that could be engineered for mass dissemination in the future because of their:</th>
</tr>
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<tbody>
<tr>
<td>• Availability</td>
</tr>
<tr>
<td>• Ease of production and dissemination</td>
</tr>
<tr>
<td>• Potential for high morbidity and mortality rates and major health impact</td>
</tr>
</tbody>
</table>
### Category A

- Anthrax (Bacillus anthracis)
- Botulism (Clostridium botulinum toxin)
- Plague (Yersinia pestis)
- Smallpox (variola major)
- Tularemia (Francisella tularensis)
- Viral hemorrhagic fevers
  -- Filoviruses - Ebola, Marburg
  -- Arenaviruses - Lassa, Machupo

### Category B

- Brucellosis (Brucella species)
- Epsilon toxin of Clostridium perfringens
- Food safety threats
  - Salmonella species
  - Escherichia coli O157:H7
- Shigella
- Glanders (Burkholderia mallei)
- Melioidosis (Burkholderia pseudomallei)
- Psittacosis (Chlamydia psittaci)
- Q fever (Coxiella burnetii)
- Ricin toxin from Ricinus communis (castor beans) NEW!
- Staphylococcal enterotoxin B
- Typhus fever (Rickettsia prowazekii)
- Encephalitis
  - Alphaviruses - Venezuelan Equine Encephalitis, Eastern Equine Encephalitis, Western equine encephalitis
- Water safety threats
  - Vibrio
  - Cholerae
- Cryptosporidium parvum

### Category C

- Nipah Virus
- Hantavirus

* Modified from the CDC*
How did we get here?

The use of biological agents is by no means new to human acts of inhumanity. There are historical records dating back to 600 BC in both in written and visual (tapestry, paintings, etc) form that document the use of exploiting biology with the same intent as of those of the present day, but their modalities were cruder. For example, one of the earliest documented uses of biological warfare, was around 600 BC when Solon of Athens used black hellebore root to contaminate the water supply of the city of Cirrha, which he was attacking. When the Cirrhaeans became crippled by severe diarrhea, they were easily defeated.

Around 400 BC, Scythian archers were noted for immersing their arrowheads in materials such as animal feces, blood, and the tissue of decomposing carcasses before knocking their arrows in combat. 200 years later, Hannibal led his Carthaginian army against the naval attack of King Eumenes of Perganum. Hannibal ordered his soldiers to fill hundreds of clay pots with snakes and then had the soldiers hurl the pots onto the decks of the Perganumese boats. Hannibal was the victor.

A common practice of biologic warfare used in the middle ages is exemplified by a Tartar attack on the city of Kaffa in 1346, in which the warriors catapulted the corpses of plague victims into the walled city successfully causing an epidemic, presumed to be Yersinia Pestis. In 1763, during the French and Indian War, Lord Jeffrey Amherst, for whom the Massachusetts town and college are named, ordered blankets known to be contaminated with smallpox be sent to numerous Native American tribes who were siding with the French. This type of practice became so common and so effective a military tactic that during the Revolutionary war, General Washington ordered
variolation of the entire Continental army. Variolation required immunization with live vaccines taken from lesions of smallpox victims, and this “protection” resulted in 1 in every 2,000 of the vaccinates developing smallpox. 8

World War I is remembered more for the utilization of chemical weapons than for biological ones, but there was extensive use of anthrax as a means of economic and political disruption via targeting of enemy livestock. However, in a sagacious and prophetic move, an effort was made to put an end to the use of biological and chemical weapons in 1925: The Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous, or Other Gases and of Bacteriological Methods of Warfare, later referred to as the Geneva Protocol. This treaty was “the first multilateral agreement extending prohibition of chemical and biological agents.” 9

By World War II, the body of scientific knowledge had grown including our understanding of microbes and microbiology. Not surprisingly, the efficacy of biological weapons grew. The military of the Japanese empire blazed the deadly trail beginning in the 1930s with its effort to conquer China, when it dropped from airplanes on at least 11 different occasions, plague-infected rice and fleas across mainland China. 10 From the 1930s through World the end of World War II, the Japanese maintained Unit 731, an aggressive biological weapons program of unprecedented proportions that was located in a usurped territory of Manchuria, China. At its peak, Unit 731 is said to have been staffed by over 3000 scientists and technicians. 11 During WWII, thousands of prisoners of war including Chinese, Koreans, Mongolians, Soviets, Americans, British, and Australians, were brought to Unit 731 as subjects for experimentation with the biological weapons being developed there including: anthrax, botulism, brucellosis, cholera, dysentery, gas
gangrene, meningococcal infection, and plague. All told, over 1000 prisoners were killed during these experiments, as documented during the war tribunals of the mid and late 1940s. The Japanese, though the boldest, were by no means alone in their efforts to develop bioweapons; nearly every major industrial power was attempting to develop such weapons to varying degrees and with varying success. In 1943, The British were frantically developing and testing anthrax bombs off the coast of Scotland for use against the Nazis. This is claimed to have been done in fear the Nazis were readying similar attacks, and the British wished to reply in kind.

Here in the United States, the biological weapons development began in force after WWII. The development, done in secret, was led by George W. Merck, of Merck Pharmaceuticals and The Merck Manual. War crime charges against the Japanese scientists who had developed and tested the biological agents on POWs were ultimately dropped in exchange for technical help with development of the US program. The focus of the research was the weaponizing of those agents that later would come to be classified by the CDC as Category A agents. As the cold war developed, another major focus was the development of molds and bacteria that were intended for Soviet wheat crops in an effort to destroy their agricultural base thereby causing food shortages as well as economic strife. Recognizing that the Soviets were developing similar weapons, the US Army ran experiments to assess American vulnerability to bioweapons attack by simulating these attacks on major cities such as New York, Saint Louis, and San Francisco, using “harmless” pathogens. After one such harmless test dispersing Serratia marcesens in and around San Francisco, 11 people became ill and one died of Serratia infections. The government claimed it was merely coincidence.
The US military also wanted to assess the feasibility of using such weapons against the Soviets and so ran ‘simulated attacks’ in Alaska because it best simulated the climatic and landscape conditions of the Soviet Union. Similar testing was done in Okinawa to determine feasibility for use in South East Asia.¹⁶

In the mid-50s, a paradigm shift occurred in bioweaponry in which biological agents that would cause incapacitation or debilitation were seen as preferable to those causing death. This shift occurred because of a concern that public opinion would more likely be supportive of the use of bioweapons if death did not result; that is, if it seemed more humane. This philosophical shift is historically significant in that it marks the rise to prominence of viruses as biological since viruses tend to be more likely to produce debilitation rather than death—probably an evolutionary adaptation to being a host dependent entity.¹⁶

The use of viruses provided other benefits from a strategic standpoint, as well. There was the added “advantage” that using viruses made antibiotic therapy irrelevant—a major obstacle in ensuring a successful attack with bacterial agents. Vaccines for the viral agents often require weeks or months to provide protection. What’s more, there are a far greater number of viruses to choose from and indeed, the US government was able to develop approximately 50 viral agents compared with only 16 bacterial agents.¹⁶ In the modern era, however, experts cite 43 viral agents, 19 bacterial, and four Rickettsia, and fourteen toxins in the arsenal of viable biological weapons.¹⁷

Another military belief was that infective agents were less useful because they were deemed to be too unpredictable and could possibly result in infecting our own troops: agents that could not be transmitted person-to-person were more manageable and
more strategic. The one infective agent that was made the exception to the rule was smallpox. It was exempted because it was so effective—highly contagious, highly durable, and easily stored, transported and dispersed.\textsuperscript{16}

Officially, the US government denied smallpox was part of the biological arsenal claiming it made an unsuitable weapon. In reality it was intended for ‘special actions’ and in fact, the Central Intelligence Agency maintained its own smallpox stock to be used at its discretion in its special operations. Ironically, during the 1960s, US government development of smallpox as a weapon was continued at the same time the government was participating in efforts to eradicate smallpox from the globe.\textsuperscript{18} Smallpox’s ‘useful’ qualities were being noted by other countries, and groups and as early as the mid 1960s, it occurred to the US officials that smallpox would be an effective agent in a bioterrorist attack against the United States.\textsuperscript{16}

It should pointed out that the breakthroughs in molecular biology and recombinant DNA technology altered the setting of the biological sciences; molecular biology was poised for the great leap forward into gene manipulation which would begin the development of more medicines and greater understanding of the science of life. However, these technologies could be applied to bioweapons and alter development dramatically, allowing for the development of “super bugs” that could be structured to be far more virulent and far less susceptible to vaccines and/or antibiotics.\textsuperscript{16} It has been said that with “the current state of research and technology, it cannot be ruled out that a potential aggressor has genetically manipulated certain characteristics of pathogens or toxins prior to their use as biological warfare agents.”\textsuperscript{19} The implications of this from a medical management standpoint are that such manipulations “could increase the
virulence, environmental stability and resistance to prophylactic and therapeutic measures.”

### Setting the Stage

Clearly, the development of the current threat of bioterrorism is rooted in the economic and political landscape of the cold war. The peak of the development here in the United States occurred in the 1960s with as many as 3500 people working on research and development of bioweapons.11

In 1969, President Nixon joined Great Britain and the Soviet Union in proposing a ban on continued bioweapons development as well as destruction of the all stockpiled weapons. The stated reason was that the viability of such weapons was minimal, but the major motivation was that the power of these types of weapons could be utilized with relatively little effort by potential enemies.15 It had been pointed out to President Nixon that because of the ease of development and relative low costs associated with bioweaponry, most countries could readily develop bioweapons. This was in stark contrast to nuclear weapons that require immense financial and technological resources that few countries have. Biological weapons have even been referred to as the “poor mans’ atomic bomb.”20 As one presidential advisor stated, the prime military concern regarding bioweaponry was “to keep other nations from acquiring them.”16 This may be what motivated the president to also mandate that a new lab be designated in which small research quantities of agents be maintained for developing adequate protective measures, diagnostic procedures, and therapeutics in preparation of a bioweapons attack. The new lab was named the US Army Medical Research Institute of Infectious Diseases
(USAMRIID). Henceforth the U.S. biological program would be confined to research on strictly defined measures of defense, such as immunization. 

The Department of Defense was ordered to draw up a plan for the disposal of existing stocks of biological agents and weapons." 21 On his order, the "United States unilaterally renounced first use of lethal or incapacitating chemical agents and weapons and unconditionally renounced all methods of biological warfare." 16

The position set forth by the US, Great Britain, and the USSR gave impetus to the United Nations document: The Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological and Toxin Weapons and their Destruction, otherwise referred to as the 1972 Biological and Toxin Weapons Convention (BTWC). It was written with the purpose of stopping the development of biological agents as weapons and to ensure the destruction of stockpiled weapons internationally. It continues to be the premiere document steering international law on this subject and has, to date, been signed by 144 countries including all the permanent members of the UN Security Council. 21

The BTWC specifies that no nation is to:

"...produce, stockpile, or otherwise acquire or retain microbial or other biological agents or toxins, whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective, or other peaceful purposes, and weapons, equipment, or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict." 21

Not surprisingly, there have been great difficulties in ensuring the BTWC is enforced. Every signatory nation is bound to submit a list of all bioweapons facilities, to list all meetings held at the facilities, to provide an exchange of information on biological warfare agents, as well as any disease outbreaks. However, no provisions were made for
oversight or enforcement of these guidelines by the UN Security Council or by neutral nations.

Much of the problem lies in the unclear distinction between military and legitimate public and/or corporate development. Such ambiguities are being refined even now, some thirty years later. Thus, the continued production by countries, among them Iraq, is one source for the availability and threat of bioweapons. In the case of Iraq, the threat (or perceived threat, depending on the perspective) is direct. However, another threat is a result of countries involved in production then selling or trading their bioweapons to the highest bidder.

The first documented occurrence of bioweapons being given to a third party was during the early 1980s when it is believed that the Soviets gave mycotoxins to the communist governments of Vietnam and Laos for use against CIA supported-resistance movements. Mycotoxins, derived from fungi, are known to be mutagenic, teratogenic, and carcinogenic. These agents are believed to have been dispersed from crop dusters over villages and cities. International relief workers witnessed the characteristic “Yellow Rains” and the subsequent elevations in distinctive morbidity and mortality patterns in the population. These reports prompted US accusations that the Soviets were in violation of the BTWC. Soil samples positive for the mycotoxin, recovered documents, confessions by local authorities, and other evidence were dismissed by the Soviets. They denied having violated the BTWC by giving the agents for use, and pointed out that mycotoxins are found naturally in these regions. The Reagan administration pressed the issued only to be cautioned that top US government scientists were theorizing that the yellow rain was a result of the feces from indigenous honeybee swarms. Doubt
remained in the West until Vladimir Passechnik, a top Soviet biologist working in their bioweapons program, spilled the proverbial beans.\textsuperscript{17}

It has since been well documented that despite their being a signatory, the Soviet Union, through the 70s and 80s, did not halt their research. Indeed, it is now known that they expanded both biological and chemical weapons research after signing the BTWC. At its zenith, the Soviet program, known as the Biopreparat, had a staff of about 60,000 working at about 50 facilities. By way of comparison, the Soviet program was nearly 20 times the size of the US program at its respective peak. It is understood, in retrospect, that the signing of the BWTC in 1972 was seen by the Soviet Union as an opportunity to gain an edge over its Cold War foes.\textsuperscript{24}

At the time, however, there was no proof of their bioweapons escalation, though the US and worldwide intelligence communities were deeply suspicious that the Soviets were actively developing bioweapons. It took an accident to get confirmation. In 1979, a presumed accidental release of anthrax from a bioweapons research facility occurred in Sverdlovsk, Russia, (now called Yekaterinburg), killing nearly 70 people of inhalational anthrax.\textsuperscript{25} Despite all evidence pointing to the likelihood of Soviet violation of the BTCW, the Soviets denied everything and accused the West of anti-Soviet propaganda. The Soviet government claimed the infections resulted from anthrax-tainted meat. There was no admission from the Russian Government until 1992.\textsuperscript{17} They have since reverted back to denial as the official position.\textsuperscript{25} Since the fall of the Soviet Union, the Russians have maintained Biopreparat though it is thought to have been scaled down considerably which, for reasons that will be discussed, is apparently a mixed blessing.\textsuperscript{15}

In 1989, the US and United Kingdom teamed up in an effort to force the closure
of Biopreparat. Inspection teams were periodically sent into Russia from 1989 to 1994. In 1994, President Yeltsin decreed that no further offensive work would be done.²⁵ Although Biopreparat was maintained after the fall of the Soviet Union, many of the biowarfare facilities were left in disrepair and many of the researchers who had been well-rewarded by the ruling Communist Party were suddenly without a job. There were and continue to be grave concerns that many of these scientists would agree to work for ‘rogue’ countries or extremist or paramilitary groups to help in the development of biological weapons programs and, furthermore, that, in exchange for handsome payments, stockpiled biological agents, including smallpox, may presently be or may already have been smuggled out of Russia or other former Soviet states into the hands of governments or subversive groups.⁶ Many feel that this is the greatest threat to keeping bioterrorism out of hands of those who might use them. The threat seems ever greater as these Russian laboratories are experiencing ever worsening financial difficulties: substantial numbers of scientists have departed and security is even more lax. Which countries and groups have actually hired these scientists is unknown, but it is well known that Libya, Iran, Syria, Iraq, and North Korea have actively been recruiting these scientists.²⁴

In order to help ensure peaceful use of technology and resources, western funding has been sent to Russia to provide bioweapons scientists with financial alternatives to accepting jobs from potential enemy states.¹⁵ Analyses by numerous nongovernmental agencies estimated the number of countries suspected to be developing weaponized biological agents at 14, most of these are in Asia, North Africa, or the Middle East.
Excluding China, most of these are “developing” nations. Including China, almost none of these countries are democracies. As mentioned, a possible threat is the use of bioweapons by a nation still producing them. Iraq is one such country in the political as well as media spotlight. At the time of this writing, the most recent war in Iraq is declared over but it should be noted that with the end of the war in Iraq in 1991, the UN Security Council resolution SCR 687 created and empowered the United Nations Special Commission (UNSCOM) to, among other things, seize all biological, chemical, and nuclear weapons found in Iraq. Initially, the suspicion that Iraq produced or even possessed was just that, suspicion. Though during the Gulf war, stockpiles of camelpox virus, which is very similar to smallpox virus, were discovered in Iraq. The Iraqis denied any intention of using Camelpox for biologic warfare. In terms of bioweapons, UNSCOM reported that for the first four years after the Gulf War, the Iraqi government denied having any involvement in the production of bioweapons and denied having acquired any bioweapons. In 1995, they acknowledged having a bioweapons development program but denied ever having actually produced any bioweapons. Soon thereafter, the head of Iraq’s military industrialization program, General Hussein Kamal Hassan, confessed the depth and breadth of the bioweapons program to western intelligence officials. Iraqi government documents indicated production of 20,000 liters of botulinum toxin and 8000 liters of anthrax spore suspension, though the United Nations believes they made closer to ten times that amount. SCUD missiles with a range of 300 to 600 km and carrying 400-lb

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*a These countries include: Algeria, China, Cuba, Egypt, India, Iraq, Israel, Libya, North Korea, Pakistan, Russia, Sudan, Syria, Taiwan,*
bombs had been outfitted with botulinum toxin and anthrax warheads, and drone aircrafts had been equipped with aerosol dispersal systems.

It was admitted by the Iraqi government that their program involved five sites for the production of human bacterial and viral pathogens as well as plant pathogens. It has since been documented that in 1988 alone, Iraq imported various strains of bacterial agents, (from a US company!) and 39 tons of growth medium for virulent agents, such as anthrax and botulinum. Six tons of this growth medium have yet to be accounted for by UNSCOM. Much of the botulinum known to be in Iraq is unaccounted for. As will be discussed later (see section on Botulinum) botulinum is the most toxic poison in existence and Iraq is thought to have possessed enough to kill everyone on the planet.

Of course, much in the way of Iraqi resources for such development comes from the US government because in mid to late 1980’s, Iraq was considered a US ally and was provided military aid in Iraq’s war with Iran. The alliance with Iraq stemmed in large part from US intelligence being concerned that the Soviets would invade the Persian Gulf in an attempt to seize control of world oil supplies. The US military had planned to respond to such an event by teaming with Iraqi forces to repel them; hence, the willingness to supply Iraq with military resources.

The seriousness of the potential threat posed by the Iraqi bioweapons program can be understood from the perspective that US bioterrorism experts indicate that Botulinum toxin, could theoretically be purified so that 3 kilograms (6.5 lbs), an amount easily transported in a suitcase, would be enough to kill the world’s population (see Section on Botulinum toxin below). It is estimated that, theoretically, only a millionth of a gram of inhaled anthrax is a lethal dose. Based on this figure, simple calculations reveal that
only about 6.5 kilograms (14.3 lbs) would be enough to kill everyone on the planet. However, it is more commonly believed that 100 kg (less than 50 lbs) would kill roughly 3 Million people—a figure comparable to the detonation of a Hydrogen Bomb.\(^{31}\)

Although the precise quantities of these agents possessed by Iraq is not known, Madeleine Albright testified to the UN that Iraq possessed, at one time, enough weaponized anthrax to kill the entire population of the world several times over.\(^{27}\) As of this writing, Iraq’s bioweapons capability is presumed by certain Western leaders to be intact. The suspicion of Iraq’s thriving, vast and oft unaccounted for biological weapons arsenal has be reaffirmed by a leading Iraqi bioweapons scientist captured in April, 2003.\(^{32}\)

In February 1989, the threat was understood and a ban was placed on the sale of bacterial agents to Iraq as well as to Iran, Libya, and Syria which were also trying to develop bioweapons.

Notably, the previous Bush Administration began to consider the possibility of these weapons being given to terrorists and smuggled into the US for use in a bioterrorism attack. For the first time in the history of the United States, the government began assembling an Emergency-Response team and developing a plan to manage such a possibility.\(^{16}\) Signed into effect by President Clinton 1995, Presidential Decision Directive 39 (PDD-39) was enacted which broadly outlines that in the event of a terrorist attack, the “crisis management,” the criminal act itself, will be law enforcement controlled and headed by the Federal Bureau of Investigation (FBI) and the Department of Justice (DOJ). It also states that “consequence management,” the public health and safety issues that result, will be under the authority of Federal Emergency Management
Agency (FEMA). All healthcare and public health involvement, clearly then, will be under the consequence management side, and thus under FEMA’s jurisdiction. In the event of an attack with biological weapons, the Department of Health and Human Services (DHHS) will be the primary federal agency for a “coordinated federal response” and the will oversee the activation of CDC activity. In anticipation of such attacks, the NIH and CDC are actively researching improved diagnostic and therapeutic modalities as well as clinical pathways to ensure diagnostic accuracy. There presently being development of a monitoring system for local ambulatory care encounter records to monitor for clustering of signs, symptoms and other findings that may indicate the result of a biological attack.

An important example of an outgrowth of PPD-39 is the establishing by the CDC, along with state and local agencies, the Health Alert Network (HAN). The HAN is a nationwide service that disseminates the latest information, provides educational services and facilitates fast and effective communication between state and local health agencies, departments and care providers for better coordination of knowledge, information, and practices in the event of an emergency of any variety.

Another is the Strategic National Stockpile (SNS), formerly known as the National Pharmaceutical Stockpile. This was another initiative coordinated by the CDC to satisfy the vaccination, prophylactic, and medical management needs in the event of a bioterrorist attack. This includes vaccines, antibiotics, medical supplies, medical equipment, etc. These resources are maintained at “strategic locations” throughout the country and are available for immediate delivery. The locales of the sites are known only by CDC officials. The NPS is structured such that it is perpetually in a state of readiness,
should a biological or chemical attack occur in the population. The supplies are packaged so that no specific request need be made; rather, a request for any particular items elicits a delivery of everything. The term used is the “12-hour Push Package” because the CDC delivers all packages in less than 12 hours, and it ‘pushes’ all possible supplies (regardless of need). It is also possible for states or municipalities to request particular items of need. On an additional note, the push package is delivered along with a team of five or six CDC advisors.

**How legitimate a threat is bioterrorism?**

According to the National Defense University, there have been more than 100 documented cases of biological agents as weapons. Of these, 19 were used by non-governmental entities for 'biocrimes.' In the months following September 11th the world experienced the relative ease with which a motivated individual or individuals could spread both infective agents and fear. All told there were 22 cases of anthrax: 11 inhalational, and 11 cutaneous. Five deaths resulted. While the American public found it hard to conceive of how such things could happen, the Defense Department (DoD) was all too clear how such a thing could happen after the ‘success’ of a scenario it created: three ‘non-experts’ were asked by the DoD to see how quickly and cheaply bioweapons could be developed: in less than 30 days and with less than a million dollars, the three were able to develop a thriving arsenal of biological weapons with “enough lethal microbes to wipe out entire cities.”

An attack on the scale of a few individuals rather than whole cities is a macabre bargain. It was recently determined by US Army scientists that the post-September 11th
anthrax attacks used an anthrax powder that was made using “simple methods, inexpensive equipment and limited expertise.” The costs involved in those attacks are thought to be approximately three thousand dollars.

Clearly then, when bioweaponry can be developed without significant financial or scientific resources this threat must be taken seriously even from individuals or small groups. The scale of infection from the anthrax attacks could have been enormous if the mode of distribution was via aerosols rather than powdered envelopes. Aerosolized anthrax would be odorless, colorless and virtually undetectable.

The threat of attack, then, stems from four possible sources:

1. The demise of the Soviet Union and with it Biopreparat has left a small army of bioweapons scientists unemployed. Some may agree or have already begun to work for nations, groups, or individuals whose intention is to use the biological weapons.

2. Along with the scientists, there are reports that the actual biological agents may have been stolen from the labs or are at least unaccounted. They may have fallen into the hands of those willing and able to use them.

3. Nations who are actively developing biological weapons may choose to use them or make them available to those who might.

4. Groups, individuals with the resources to make or acquire biological weapons with the intent to use them in an attack.

Primary Care and Bioterrorism

A survey conducted by the Agency for Healthcare Research and Quality (AHRQ), a branch of the Department of Health and Human Services (HHS), found that 75% of
primary care doctors did not feel prepared to deal with infections from biological agents; nor did they feel prepared to identify an illness from a biological agent even in their own patients.41

Bioterrorism presents a number of challenges for the primary care physician. The events of September 11th and the unsolved anthrax attacks created a certain level of fear and anxiety. As a community practitioner, community member and leader, the primary care physician will be looked to as a source for answers regarding the myriad of questions relating to bioterrorism, and as a comfort for the anxieties and tensions.42

More than that, the primary care physician will be a sentry, watching for the index case(s) that indicate bioweapons use. In turn, initiating and participating in the public health response to such an attack will be an important role for the primary care physician. This will require not only diagnostic vigilance but also an understanding that being a community physician means needing to be tapped into the public health structure, staying informed on the latest updates of management, diagnostic techniques, response plans for the city, state and federal agencies.43

Should the primary care physician make or even strongly suspect a diagnosis, many important considerations will arise including medical management of the patient and possibly of their family or household contacts; notification of public health officials on all levels; proper means of infection control; issues of vaccination, prophylaxis not only for the primary care physician but staff as well. The considerations are great and the choices not always so clear.

As will be discussed later, diagnosis of infection from biological agents is not always so easy, particularly early in the disease course as the presentation of many of the
biological agents can be non-specific. What’s more, if the infected person is seen early on or particularly as the index case, recognition will indeed be difficult. Once an index case is found, the CDC and other public health officials will begin mobilizing and subsequent awareness and vigilance will be heightened, thus easing the physician’s burden while also simplifying the management. “Once an outbreak is identified, then it is relatively easy to disseminate information on the nature of the infectious disease agent, in terms of its recognition and control.” It is precisely because the onset of symptoms presents non-specifically, and because these symptoms are often ‘flu-like’ or somewhat benign, that there is a high likelihood the index cases will be seen at the office of a primary care physician.

There is a commonly held belief about how a bioweapons attack would play itself out in the US, and most experts presuppose that the event will occur in the form of a large scale, catastrophic event, which would immediately illicit activation of an emergency response system of emergency departments and public health officials. This view is reflected in the emphasis being placed in terms of response both at the federal and state level. For example, in the past 6 months, the Connecticut Department of Public Health has posted five “Public Health Advisories,” all related to smallpox vaccination and only one mentioned primary care physicians. Similarly, the CDC’s website on “Bioterrorism: Training” has just one link specific to clinicians, and at their webpage “Preparation and Planning” has no offerings for outpatient clinicians. It’s quite clear then that primary care physicians are overlooked both in terms of training needs and as a part of the public health infrastructure. Such oversight is affirmed by a simple Medline search: “bioterrorism” and “primary care” elicits 6 titles. In contrast, “bioterrorism” and
“emergency” elicits approximately 200 titles. In one sense this is appropriate, as the use of biological agents would indeed require emergency responses of all kinds. However, as is argued in this paper, though it may become an emergency it will likely begin quietly in the outpatient setting. By making primary care physicians better equipped to identify, manage, and involved in bioterrorism, the resulting emergency identified sooner, less severe, contained faster, and, involve fewer victims.

What’s more, numerous scenarios that have been postulated tend to hinge on a dramatic event that initiates the attack or by diagnosis in the ED. Some of these scenarios were developed by the CDC while others were developed by the Center for Civilian Biodefense Strategies (CCBD). Even with such a scenario, it is still quite likely that index cases will present in outpatient clinical settings—again, in part because of the non-specific initial symptoms, but also because of the incubation time (depending on the agent). Another contributing factor in patients seeking out their primary care doctor is the pre-existing relationship between doctor and patient. A patient, even in the context of an attack, may feel most comfortable or give first thought to seeing their primary care physician with whom they have a relationship, particularly if the patient is confused, sacred or even panicked.

It has been pointed out that even if there is a large-scale attack, the initial case will present as isolated incidents or with surprisingly low numbers. Many feel that primary care providers will be “sentinels at the gate.” But even if a dramatic event occurs, community physicians, were they properly trained utilized, could be an invaluable means of helping to contain outbreak.
On the other hand, it is just as likely that future bioweapons attacks would occur similarly to the way it occurred with the anthrax attacks in the two months following the events of September 11th when, over the course of 47 days, 22 cases of anthrax occurred. Of the 22 cases, five were fatal. With this attack, there were no bombs dropped, no dramatic pronouncement or Hollywood chaos. Instead, it was simply numerous mailings of card-sized envelopes with the proper postage.48 “A bioterrorist attack is likely to be covert - we will know we have been attacked only when people begin to get sick and seek medical attention.”49 In the index case of the anthrax attack in 2001, the victim, a 63 year-old man, presented to the emergency department of a Florida medical center on October 2nd, and was diagnosed with anthrax on October 4th. Four days prior to admission the patient was in good health and had left for Florida on a short vacation. On the first day of his trip he began to feel fatigued, noticed a sore throat, nausea, and a low-grade fever.50

Any primary care physician sees countless patients each week complaining of similar symptoms, especially in October and all though the fall and winter months. The index anthrax patient could have very easily decided (or been persuaded by his wife) to have gone to his primary care physician back home or have sought one out while on his trip in Florida. Would a primary care physician have picked up on the diagnosis or would he or she instead have reassured him, given him some acetaminophen and sent him on his way? By October 2nd, his symptoms were severe and the emergency department was the right place for him to be.

In either of these two scenarios or in any other scenarios, diagnosing the index case will be extremely difficult and will only be made in a timely way if primary care physicians maintain a baseline level of vigilance.
The following is an attempt to make proper and timely diagnosis more likely by serving as a resource for primary care physicians. Included is information regarding means of transmission, basic diagnostic information including: signs and symptoms, laboratory findings, radiographic findings as well as means of differentiating naturally occurring forms of infection versus weaponized forms.

Recommendations for appropriate use of prophylaxis and protective measures for the primary care physician and his or her medical/office staff, as well as the patient’s close contacts will be discussed, as will what historical information is to be obtained from the patient. When possible, distinctions are made between the classic or ‘natural’ clinical features of these microbes and the distinctive clinical features resulting from the weaponized forms of the microbes. In either form, there is, on the whole, a minimum of available data since most of these agents are no longer naturally occurring with any great frequency.

Throughout the descriptions of the agents and their diagnoses, is additional information that may well be needed for answering commonly asked questions about bioterrorism on the whole and about specific agents, in particular. Included as well are online resources for patients and clinicians as well as key contact information.

**Category A Agents**

**Anthrax**

Anthrax (Bacillus anthracis) is a gram-positive, non-motile spore forming bacterium that infects both humans and animals, particularly livestock. Anthrax is found in a worldwide distribution. The spores, most commonly found in soil, are quite hardy
and able to survive for decades under ambient conditions. However, in vitro, spores will not form unless body fluid is exposed to ambient air.\textsuperscript{51}

Background

The name ‘anthrax’ is derived from the Greek word meaning “coal,” because of the black skin lesions it can cause. Anthrax has been present throughout human history with the first record of it being seen in the Old Testament-Book of Genesis as the 5\textsuperscript{th} of the 10 plagues purportedly sent down by the God of the Jewish slaves. The Roman poet Virgil wrote verse describing the disease in 25 BC.\textsuperscript{52}

The incidence of anthrax has dropped significantly over the years in technologically advanced countries, in large part because of vaccination of those at high risk—those regularly exposed to hides, wools, and other raw livestock products.\textsuperscript{52} Prior to the anthrax attacks in 2001, experience with anthrax was limited. In fact the only modern experience with the inhalational form was the accidental release of anthrax spores from the Soviet Bioweapons facility in Sverdlosk, Russia.\textsuperscript{31}

Epidemiology

In the US, there have been no cases of inhalational anthrax in the past 20 years and only 18 cases in the past century. There have been only 127 cases of anthrax in any form in the US during the 20\textsuperscript{th} Century. There are between 20,000 and 100,00 cases of anthrax worldwide, almost entirely in developing nations; needless to say, information is limited.\textsuperscript{51} Most current public health policies, such as vaccines, as well as medical management practices are based on limited information and are ever evolving.\textsuperscript{24} The mortality rates for inhalational anthrax are greater than 80\% however, this figure was
arrived at prior to modern antibiotics and the advent of critical care resources. The post-September 11th inhalational anthrax patients had a mortality rate of 40%. 53

Means of transmission.

Infection can occur from either direct contact with active bacteria or indirectly from contact with spores which then germinate. The spores may be in animal hair, meat, hides, or other products. The weaponized form of anthrax is constituted in the spore form and may be maintained as powder, such as with the post-September 11th attacks, or may be in an aerosolized form. Anthrax infections can take three forms: Inhalational, Cutaneous, and Gastrointestinal. 51 For all three, the basic pathophysiology of the bacteria is the same; however each is different in terms of the local effect and in terms of morbidity and mortality. Each of the three will be discussed individually.

Pathophysiology

General: B. anthracis derives its virulence from its being encapsulated and as a result of three secreted proteins: Protective antigen, lethal factor, and edema factor. Protective antigen facilitates the binding of the bacteria to host cell membranes and subsequent transport intracellularly of the other two toxins. 51 Edema toxin acts to inhibit neutrophils as well as causing edema by disrupting water homeostasis. Lethal toxin causes activation and dysregulation of cytokines such as Interleukin-1 and Tumor Necrosis Factor. 31
Figure 1 Anthrax microscopy

Picture courtesy of University of Wisconsin-Department of Bacteriology
Notice the ‘box car’ like appearance

Microscopy

Identifying features include: Gram-positive rods measuring approximately 1-1.5x 3-5 microns singly or in chains, with a “bamboo” or boxcar appearance (see figure 1). General features include non-motile, non-hemolytic, and encapsulated bacterium (easily demonstrated with India ink culture). Spores-The spores are “oval, central, or subterminal spores” that grow readily on all ordinary laboratory media at body temperature, they measure 1-1.5 microns, however, no increase in bacterium size may be noted; these are best seen in those cultures in which nutrients have been previously consumed.  

While few laboratories specialize in bioweaponry, diagnosis can generally be made based on the features of B. anthracis: gram-positive, penicillin sensitive, spore-forming bacillus. However, polymerase chain reaction (PCR) and other assays will ultimately be needed for confirmation. The active bacteria may be handled in a Biosafety Level (BSL)-2 laboratory- that is, a standard clinical laboratory that practices "universal"
precautions and has facilities for minimizing aerosols. However, spore handling requires
BSL-3 laboratories.\textsuperscript{54}

\textit{Inhalational Anthrax}

\textit{Pathophysiology}

Since the spores range from one to five microns in size, they easily reach the
alveolar spaces within the lung with inspiration. The spores are quickly engulfed by
macrophages thus destroying most of the spores, however, some manage to survive. The
surviving spores are taken up by the lymphatics and arrive at the mediastinal lymph
nodes at which time the spores undergo germination. It should be noted that germination
may not occur for upwards of six weeks and have taken up to as many as 12 weeks in
some primate studies.\textsuperscript{31} Once germination begins, symptoms will appear rapidly.
Symptom onset is a result of bacterial toxin release causing necrosis, edema, and
hemorrhage. It is the toxin level that is associated with mortality. This is significant
because a negative blood culture does not necessarily mean the patient has reached a
point of improvement. Pathologically, no bronchopneumonic processes are noted in
inhalational anthrax.\textsuperscript{51}

\textit{Transmission}

Classically, spores located in the soil or in contaminated animal products are
kicked up into ambient air and inhaled directly into the respiratory tract. Because of their
small size, they are able to arrive in alveolar spaces. It is worth mentioning that it had
been thought that the LD\textsubscript{50} (The dose adequate to kill 50\% of those exposed) was
between 2,500 and 55,000 inhaled spores. While no LD\textsubscript{50} has been determined, it’s felt
that of the deaths that occurred from the post-September 11th attacks, the LD<sub>50</sub> was considerably lower.\textsuperscript{31}

\textit{Signs and symptoms}

Classically, inhalational anthrax follows a biphasic pattern (early and late) or may exist as a continuous process. The post-September 11th anthrax patients presented in this biphasic pattern.\textsuperscript{51}

Early (stage I-lasting hours to days): The presenting clinical findings in 10 out of 11 of the September 11th victims were myalgia and fever. On the whole, their signs and symptoms were consistent with the signs and symptoms seen in the zoonotic form. These signs and symptoms include fever, myalgia, non-productive cough, nausea, vomiting, diaphoresis, dyspnea, myalgia, chest pain, headache, and tachycardia. Other symptoms associated include chills, and abdominal pain.\textsuperscript{54}

Late (Stage II): Respiratory paralysis, diaphoresis, cyanosis, sudden fever, hypotension, respiratory alkalosis, and terminal acidosis, massive lymphadenopathy, hemorrhagic meningitis (often with concurrent meningismus), delirium, and obtundation. This stage is rapidly progressive with shock, hypothermia, and death occurring within 24-36 hours.\textsuperscript{31}

\textsuperscript{51} The transition from stage I to stage II can occur suddenly-as a continuum or even after a short period of improvement. Classically, Stage II is reached with 2-3 days from onset of Stage I.\textsuperscript{54}

\textit{Microscopy}

Generally, neither sputum culture nor blood culture will be of diagnostic value with inhalational anthrax primarily because there is little in the way of pneumonic
processes. Once bacteremia and/or systemic infection occurs, staining and culture may be of value.\textsuperscript{54}

*Lab findings*

Early-none (including no or minimal elevations in WBC)

Late-Hypocalcemia, hyperkalemia, hypoglycemia can be seen. Increases in hemoconcentration are seen with hematocrits often greater than 50\%\textsuperscript{.53}

*Radiographic findings*

Inhalational anthrax is characterized by a series of radiographic and tomographic changes that can greatly aid in diagnosis. These are summarized in tables 2 and 3, respectively. The post-September 11\textsuperscript{th} anthrax patients were found to have some or all of the features discussed below:

*Figure 2 Anthrax-Chest X-ray at presentation*

![Radiograph of chest x-ray showing widened mediastinum, right hilar enlargement/mass (arrow), right pleural effusion, and right perihilar airspace disease.](image)

*Courtesy of Earls JP Radiology 2002 Feb; 222(2): 305-12*

The findings include a widened mediastinum, right hilar enlargement/mass (arrow), right pleural effusion, and right perihilar airspace disease.
Effusions and air-space disease increased dramatically over the initial several days. Effusions re-accumulated several times necessitating repeated thoracentesis.

**Computed Tomography**

All CTs taken of the post-September 11th anthrax patients showed abnormalities. There is historical and medical significance to the CT findings. Because of the rarity of inhalational anthrax in the modern era, and particularly since the advent of CT scans, no CT-studies had been published prior to the post-September 11th anthrax attacks. The results are corroborative of the classic chest X-ray findings and CT is now considered an important tool in diagnosing anthrax.\(^{55}\)
Figure 4 Anthrax-Chest CT at Presentation

Widespread hyperattenuating adenopathy (key diagnostic feature)
The largest lymph node (arrow) is in the subcarinal region

Figure 5 Anthrax-Chest CT Day 4

Effusions were considerably larger and filled more than 50% of each thoracic cavity
Note the bilateral moderate-sized pleural effusions, and bibasilar air-space disease peribronchial thickening (arrows).

Note the peribronchial thickening (arrows).

**Table 2** Key radiographic findings—Chest X-ray

**Chest X-ray—key diagnostic features of Anthrax**
Radiographs provide critical diagnostic information many hours or even days before blood and sputum cultures can be used to confirm the presence of anthrax. However, please note that radiographic changes may appear late, which indicates a poor prognosis.

**Characteristic chest X-ray findings:**
- Presence of a widened or abnormal mediastinum
- Hilar adenopathy
- Pleural effusions
- Peripheral air-space disease
Table 3 Key radiographic findings-CT

Chest CT—key diagnostic features of Anthrax
Initial CT studies in virtually all of the post-September 11th inhalational anthrax cases were markedly abnormal and had an unusual combination of findings that are believed to be useful for diagnosing inhalational anthrax. These cases are the first correlative study of CT and inhalational anthrax. CT appears to be a promising tool or making diagnosis.

Characteristic chest CT-findings:
- Enlarged hyperattenuating mediastinal and hilar lymph nodes
- Diffuse edema of mediastinal fat
- Peribronchial thickening
- Pleural effusions

Differential diagnosis—based on symptoms: pneumonia, influenza, viral syndrome, sepsis, bronchitis, central nervous system (CNS) infection, and gastroenteritis.

Differential diagnosis—based on radiographic changes: histoplasmosis, sarcoidosis, tuberculosis, and lymphoma.

Diagnosis:

Early diagnosis requires a very high index of suspicion because of the non-specific nature of the early symptoms. Inhalational anthrax is particularly hard to diagnose particularly because it may be hard to distinguish from pneumonia, which is orders of magnitude more common. Yet, early diagnosis is vital for successful management. This cluster of symptoms described above—especially fever or sepsis along with consistent radiographic changes in an otherwise healthy patient requires that anthrax be considered in the differential.

In the event of an epidemic, nasal swabs may be taken from those with possible exposure and any positive results necessitate prophylactic antibiotic regimen. Please note
that neither the sensitivity nor the specificity of nasal swabbing has been ascertained. A negative result does not rule out the possibility of infection.51

Because the natural course of germination and replication is occurring in the lungs, distinctive clinical features are seen: Pleural effusions, lymphadenitis, hemorrhagic mediastinitis.31, 51

Table 4 Key diagnostic features of Inhalational Anthrax

Making the diagnosis of Inhalational Anthrax

- Pattern identification: 1. Multiple, concurrent cases of an afebrile illness that progresses rapidly to death.
  2. Afebrile illness seen in high-risk groups (see Table 19) following a following an identified attack

- Presentation: afebrile, pneumonia-like presentation

  CT: Enlarged, hyperattenuating hilar and mediastinal nodes, mediastinal edema, peribronchial thickening, and pleural effusions.

Modified from 31

Prophylaxis

Inhalational

Recent studies on animal models have shown that the anthrax vaccine offers protective value against the inhalational form of anthrax, while humans studies have shown protection against the cutaneous form. The vaccine is an acellular filtrate of an attenuated form of the bacteria and given in a series of six doses at 0, 2, and 4 weeks, then 6, 12 and 18 months, followed by yearly boosters. It’s been shown that protection is attained after even two doses.56 Studies indicate it is relatively safe with about one percent of people developing some kind of minor reaction; a headache being the most
common no long-term sequalae has been reported. When given with proper antibiotic therapy, there is protection against development of the disease even after exposure. Current stockpiles of the vaccine are limited and no increases in production are expected. At present, vaccination is given only to those in the military. While the post-September 11th anthrax patients were not given the vaccine however, a number of people deemed to at risk for possible exposure were given the vaccine along with antibiotic therapy (see Appendix C for full list and for dosing schedules). 31

Prognosis

Because of so few cases of anthrax- particularly inhalational- no clear factors can be associated with morbidity and mortality. All that seems clear at this time is that early recognition with initiation of combination therapy (see section on management below) appears to be key for survival. Among the post-September 11th anthrax patients, those who presented with fulminant anthrax before antibiotic therapy was initiated died (see section on treatment below). 31

Cutaneous Anthrax

By far, the most common naturally occurring form (over 95% of all cases), the cutaneous anthrax is usually results from direct contact with infected livestock or livestock product. 51,31 This form could be seen in a biological attack particularly in a powered form as was used after September 11th (11 of the 22 cases were cutaneous). 31 Left untreated the mortality rate is approximately 20%. With appropriate antibiotic coverage, mortality is less than 1%. 53
Transmission

Infection results simply from bacterial contact with skin particularly if any abrasions or openings are present. Exposed skin surfaces are, of course, the most common sites. Incubation period appears to be short: usually less than two weeks after exposure (versus inhalational). Recognition of the cutaneous form may be crucial because it may the first and best evidence that an attack with anthrax has occurred. On an historical note, it is believed that one of the September 11th hijackers was seen by a Florida physician for what was initially diagnosed as a skin infection but was later (during the September 11th attack investigations) diagnosed as cutaneous anthrax. A proper diagnosis initially might have altered history—further highlighting the importance of properly training outpatient clinicians.

Pathophysiology

The same three virulence factors that act in the lung in inhalational anthrax act cutaneously at the site of contact.

Signs and Symptoms:

Early- Classically, there is a painless, pruritic, papular primary lesion that forms with one week of exposure to the endospore. The papule has commonly been mistaken for an insect bite, initially. Within 2 days of papule eruption, 2-3 mm vesicles form around the papule containing serous or serosanguinous fluid (contaminated with numerous bacilli and the occasional WBC). These vesicles may grow and often satellite vesicles appears. The site may become highly edematous, but non-pitting, secondary to the release of edema toxin by the bacteria. The lesion ruptures, enlarges, and becomes necrotic forming an ulcer covered by the black eschar for which the disease is named. See
figures 8 and 9 below. The eschar then dries up falls off within two weeks. Also often accompanying the lesion is lymphadenopathy. Secondary infection with Staph aureus is unusual but, if present, will manifest with painful lymphadenopathy, purulent discharge, and lymphangitis. Concomitant low-grade fever and malaise are quite common are more likely with more extensive lesions.

**Figure 8** cutaneous anthrax - day 4

**Figure 9** cutaneous anthrax day 7, day 15

Day 7(left), day 15 (right)

Late- Occurring rarely, systemic disease is a late and advanced manifestation of cutaneous anthrax. It is seen with bacteremia, renal failure, anemia, bleeding and ecchymoses is possible.

*Labs*

Early- no significant changes.

Late- microangiopathic hemolytic anemia, coagulopathies, hyponatremia.
Pathology

Any vesicular fluid should be sampled and gram stained, or if the patient is on antibiotic therapy already, a punch biopsy should be taken of the lesion.

Differential diagnosis

Tularemia, plague, scrub typhus, anticoagulant necrosis, Rickettsial spotted fevers, rat bite fever, and ecthyma gangrenosum, vasculitides, arachnoid bites, leprosy, Lymphogranuloma venereum, chancroid. 59

Diagnosis

As with the inhalational form, early diagnosis is very difficult and requires a high index of suspicion. However, the black escharic lesion is strongly suggestive particularly in an edematous setting. 53

Table 5 Key diagnostic features of cutaneous anthrax

<table>
<thead>
<tr>
<th>Making the diagnosis of Cutaneous Anthrax</th>
</tr>
</thead>
</table>
| • Pattern identification: 1. Multiple, concurrent cases of a maculopapular lesion that forms an eschar; regional adenopathy. Prodromal symptoms may be seen  
  2. Illness with maculopapular lesion that becomes escharic seen in high-risk groups (see Table 19) following an identified attack |
| • Presentation: initial painless, pruritic papular lesion that drains, enlarges, ulcerates and forms an eschar that falls off in 1-2 weeks, Low-grade fever and malaise may be seen. |
| • Findings: Escharic skin lesion. |

Treatment

It should be noted that antibiotic therapy does not alter the natural history of the skin lesion but does reduce the likelihood of systemic disease occurring. Untreated, mortality from cutaneous anthrax is around 20% (see Appendix C for full antibiotic regimen). 31
**Gastrointestinal anthrax**

*Transmission*

Transmission is not clearly understood but is believed to result from either ingestion of the vegetative form of anthrax from the consumption of undercooked, infected meat or by spore deposition in proximal portion of the gastrointestinal (GI) tract. If infected via spores, it is likely that inhalational anthrax infection may also be present. No cases of GI anthrax were diagnosed among those infected in the post-September 11th anthrax patients.\(^{31}\)

*Signs and symptoms*

Onset of symptoms classically begins within 2-5 days of ingestion. If the upper GI tract is affected, oral or esophageal ulcers form with regional lymphadenopathy, edema, and sepsis. In the lower GI tract, intestinal lesions form usually in the terminal ileum or cecum resulting in nausea, vomiting, malaise, bloody diarrhea, acute abdomen, or sepsis. Hemorrhagic mesenteric lymphadenitis can be seen as a later development as can ascites. Systemic disease may develop and yields the same array of signs and symptoms as found in the systemic forms of inhalational and cutaneous infections.\(^{60}\)
**Table 6** Key diagnostic features of gastrointestinal anthrax

<table>
<thead>
<tr>
<th>Making the diagnosis of Gastrointestinal Anthrax</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pattern identification: 1. Multiple, concurrent cases of:</td>
</tr>
<tr>
<td>a. vomiting, bloody diarrhea, acute abdomen</td>
</tr>
<tr>
<td>b. oropharyngeal ulcers with adenopathy</td>
</tr>
<tr>
<td>2. GI symptoms seen in high-risk groups (see Table 19) following an identified attack</td>
</tr>
<tr>
<td>• Presentation: early vomiting, bloody diarrhea, acute abdomen, later-sepsis;</td>
</tr>
<tr>
<td>possible oropharyngeal ulcers with adenopathy</td>
</tr>
<tr>
<td>• Findings: UGI series: Widened mediastinum, infiltrates, pleural effusion.</td>
</tr>
<tr>
<td>CT: mesenteric lymphadenitis, ileocecal ulcers</td>
</tr>
</tbody>
</table>

**General Considerations on Anthrax**

Though occurring far more commonly in inhalational anthrax, progression to systemic disease will occur in any of the forms if left unrecognized, and therefore untreated. Based on the management of the post-September 11th anthrax patients, blood cultures can become sterile after one dose of antibiotics, making it even more critical than usual that blood cultures be drawn prior to antibiotic administration.\(^{54}\)

**Diagnostic Considerations**

If anthrax is suspected or even on the differential, the laboratory should be notified as a protocol set forth by the CDC needs to be followed to ensure proper diagnosis.\(^{31}\) The context of patient illness is of critical importance. As evidenced by the post-September 11\(^{th}\) anthrax patients, certain groups are at higher risk: Postal workers, mail room workers, media personnel, politicians and their associates, microbiology lab personnel, those who have had recent contact or proximity to politicians, federal, state or local, government employees, as well as visitors to monuments or government buildings, visitors to prominent media institutions, etc. That is to say, the importance of taking a thorough and relevant history cannot be emphasized enough including the often-
neglected travel, occupational, and social histories. Obviously, clustering of cases with similar signs, symptoms and other findings, particularly if traceable to a single foci such as a building is highly suggestive of a biological attack.\textsuperscript{54}

In any unexplained death in which anthrax is a possible cause, it is imperative that an autopsy be done. A finding of hemorrhagic necrotizing mediastinitis or hemorrhagic necrotizing lymphadenitis is considered pathognomonic for inhalational anthrax. Hemorrhagic meningitis is highly suggestive of a systemic anthrax infection.\textsuperscript{31}

\textit{Treatment}

Precisely because of the limited experience with anthrax, and because there exist no clinical studies, treatment guidelines are far from definitive. What is generally agreed upon is that because of the rapidity with which symptoms set in and progress, particularly with inhalational anthrax, early administration of antibiotic therapy is vital. Thus, any person who is at high risk for possible exposure to anthrax must be put on antibiotics covering anthrax.\textsuperscript{31}

Presently, Ciprofloxacin is FDA-approved for treatment of inhalational anthrax. Ciprofloxacin, doxycycline and penicillin G Procain are approved for use in post-exposure prophylaxis of inhalational anthrax. Doxycycline and penicillin G Procain are approved for use in cutaneous and gastrointestinal anthrax.\textsuperscript{61}

FDA approval notwithstanding, the CDC and The Working Group on Civilian Biodefense (WGCB)\textsuperscript{b} recommendations are that for inhalational anthrax a multidrug regimen of ciprofloxacin or doxycycline plus another antibiotic that is likely to have

\textsuperscript{b} The WGCB is an expert panel including 23 representatives from academic, government, and private institutions with expertise in public health, emergency management, and clinical medicine convened by the Center for Civilian Biodefense Studies at the Johns Hopkins University Bloomberg School of Public Health to develop consensus-based recommendations for measures to be taken by medical and public health professionals for certain biological agents that may be used civilian populations. The term ‘recommendations’ as used in this paper, refers to Working Group recommendations.
sensitivity such as rifampin, vancomycin, clindamycin, and aminoglycosides (see Appendix C for full list and for dosing schedules). 53

After susceptibility testing, the regimen should be altered appropriately to include not only the most efficacious but also the least toxic antibiotics available. Recommendations, at present, are that treatment continue for 60 days because of the risk of recurrent disease from delayed spore germination, however once the patient is clinically well enough, parenteral administration can be changed to oral administration (see Appendix C for dosing schedules). Thoracocentesis may be indicated depending on the clinical scenario.31

Cutaneous anthrax

Although, penicillin has traditionally been used to treat cutaneous anthrax, current recommendations are for either ciprofloxacin or doxycycline for 60 days. Occupational sources of cutaneous anthrax need only be treated for 7-10 days; however if inhalation of spores is possible, then the 60-day antibiotic regimen is needed. In the case of a possible bioterrorist anthrax attack, cases of cutaneous anthrax must be presumed to have concurrent inhalational exposure.61 It should be noted that antibiotic therapy will not prevent formation of the cutaneous lesions, but will prevent systemic infection. No topical therapy is indicated.31
Gastrointestinal anthrax

Current recommendations are to follow the same drug guidelines as those for inhalational anthrax.

Post-Exposure Prophylaxis

Current recommendations are that any asymptomatic people with likely exposure to anthrax should be treated prophylactically with oral administration of ciprofloxacin or doxycycline for 60 days to ensure preventing infection from delayed germination of spores.61,31

Further Treatment Considerations

• While samples taken from patients from the post-September 11th anthrax attacks showed susceptibility to each of the three FDA approved treatments, weaponized strains of anthrax are known to have been developed which possess resistance to each of these.31
• There is no clinical basis for recommending the use of multiple versus single drug regimens, but it is felt to be a reasonable therapeutic approach by the WGCB.
• If meningeal involvement is known suspected, ciprofloxacin is preferred over doxycycline because of its improved CNS penetration, with additional coverage of penicillin, rifampin, or chloramphenicol.
• Adjunctive therapies such as steroids, Anthrax IgG antisera, tumor necrosis factor (TNF) inhibitors, anthrax vaccine, etc., may have a role in improving the anthrax patient’s condition however there are no clinical studies to support there use in this context.
Zoonotic forms of anthrax cannot be spread from person-to-person, nor does it appear that in the post-September 11th anthrax patients did any patients become infected from person-to-person transmission. Standard barrier isolation is recommended for the in-patient setting, however, neither air filtration systems nor masks are indicated. There is no indication for administering anthrax vaccine or prophylactic antibiotic therapy to any contacts of the patient including family, friends, medical providers, etc. Only those who are likely to have had similar exposure as the patient are candidates for prophylaxis.

The laboratory to be used must be notified so that appropriate handling measures can be in place. Local, State, and Federal public health officials must be notified (See discussion on Notification further on).

Standard antimicrobial cleansers such as hypochlorite may be used for cleaning up any bodily fluids that may be infected.

Botulinum toxin

Botulinum toxin includes seven different proteins (identified A- through G) that are secreted by four distinct but closely related types of Clostridia bacteria. C. botulinum is a spore-forming, obligate anaerobe found most commonly in soil.

Background

Botulinum is the most potent toxin in existence. Theoretically, one gram, properly dispersed would kill over a million people. It is colorless, odorless, and said to be without taste. An outbreak of botulinum is considered a medical emergency and will
entail the use of antitoxin as well as the likely utilization of life support systems.

Botulinum toxin as a weapon of bioterrorism posses some distinctive features from the other Category A agents. To begin with, it is the product of a microbe and not the microbe itself that is virulent.\(^\text{62}\) Strangely enough, botulinum is the only biological toxin approved for therapeutic uses in the treatment of such conditions as tetanus, blepharospasm, strabismus, etc.\(^\text{13}\). It is also approved for use cosmetically in the treatment of wrinkles. Although unapproved by the FDA for these, it has been used for treating migraines, chronic back pain, achalaisa, and other conditions.

Historically, many of the deaths associated with botulism were a result of exposure from improperly prepared and canned foods.\(^\text{63}\)

As a weapon, botulinum is far more potent (per equivalent weight) than any synthesized chemical toxins, and is considered the most toxic substance (ounce for ounce) known to humanity. Acts of terrorism involving botulinum have already occurred, with three separate attacks all in Japan including one at a US military base. Fortunately, none of the attempts were successful. Of note, the botulinum used in these attacks was made from clostridium cultures that were grown from local soil samples. All four of the designated members of the “Axis of Evil” are believed to presently possess or have begun production of botulinum.\(^\text{29}\)

Through automated processes, large quantities of botulinum can be produced and introduced in an attack in aerosol form or through contamination of the food or water supplies (though no waterborne illnesses have ever been reported with botulinum). Inhalation results in a similar presentation to foodborne infection, but the slower absorption rare though the intestinal mucosa results in a slower onset of symptoms.\(^\text{29}\)
There are three naturally occurring forms of botulism: foodborne, wound, and intestinal. An additional form, resulting from the weaponization of botulism is: inhalational.63

_Epidemiology_

Natural outbreaks are rare. Based on patterns from natural occurrences, there are less than 200 cases (including all forms) each year in the US with equal distribution between men and women and ages. Foodborne botulism results in roughly nine cases per year and outbreaks average 2.5 cases. The largest foodborne outbreak was in 1977 at a restaurant in Michigan with 59 cases.29 Of the seven forms of botulinum toxin, A, B, and E are most commonly seen in humans. F is rare; C and D are more common in non-humans and G does not appear pathogenic.62

_Means of transmission_

All three naturally occurring forms result from Clostridium synthesis of botulinum either in vivo or prior to entering the bloodstream. Botulinum enters the body via absorption through the mucosal linings of the gastrointestinal tract or the respiratory tract or from a contaminated wound. Botulinum cannot enter the body through intact skin. A bioterrorist attack with botulinum would likely be from an aerosolized form although it is possible that it could occur through contamination of food or water. Some protection is offered by simply covering one’s mouth with thick or folded cloths such as a handkerchief (see Patient Questions section below). Fortunately, sunlight denatures the toxin rendering it harmless within 1-3 hours of exposure and the chlorine content of most municipal water supplies inactivates approximately 85% of botulinum toxin.63 Foodborne outbreaks, natural or deliberate, require foods that are uncooked or are poorly cooked.
Natural infections tend to occur from contaminated vegetables- and particularly those that have a relatively high pH, such as beans, corn, carrots and peppers. The mortality rate in the modern era is less than 5%. 

Neither botulism nor botulinum is infectious; they cannot be passed from person-to-person. 

However, a theoretical risk exists for transmission. It is now known that the Soviets had been experimenting with splicing the Clostridium gene that codes for botulinum toxin into an infectious bacterial agent. Accomplishing this would effectively create an infectious form of botulinum. Whether the Soviets (or others) were successful in their efforts is not known. 

*Pathogenesis.* 

Once inside the bloodstream, the toxin will bind at neuromuscular junctions in the periphery. The biological effects of botulinum toxin are a result of polypeptide chains: A and B. The B subunit binds irreversibly to the pre-synaptic motor neuron. The toxin is endocytosed into the terminal end of the axon. Once inside, subunit A functions to cleave the SNARE proteins-the proteins involved in the release of acetylcholine (Ach) into the synaptic cleft. Consequently, no Ach reaches the post-synaptic neuron and, therefore, the neuron cannot be activated. Motor paralysis results. Botulinum toxin cannot cross the blood-brain barrier. 

*Signs and symptoms* 

All forms of botulism present with the same general signs and symptoms. Foodborne botulism may begin with nausea, vomiting, cramping, or diarrhea but this is believed to be unrelated to botulinum toxin and rather a result of other Clostridial
metabolites. Such a distinction is noteworthy because even if a bioterrorist attack involved contaminated food or water, only the neurological effects will be seen as it will purified toxin and no Clostridium will be present. So, regardless of the mode of attack, the presentation will be same.²⁹

Onset of symptoms is seen between 12-36 hours after exposure depending on the extent and amount of exposure. In animal studies, low doses have been shown to take up to a few days prior to onset of symptoms, and in higher doses, symptoms are seen in well under 12 hours. It is important to note that there can be extreme variation in the scope and timing of symptoms. However, all cases from mild to severe will include cranial nerve (CN) paralysis since the toxin always affects bulbar musculature (see table 7 for clinical features).²⁹

Early- CN Palsies, especially those affecting the eyes and the oral pharynx, are noted (See figure 10a, b). Patients seek medical care for one or more of the following complaints: difficulty seeing, speaking and swallowing. Next affected are the skeletal muscles which become weak and show a diminished deep tendon reflex (DTR) and undergo flaccid paralysis—occurring in a symmetrical, descending and progressive pattern (with accompanying loss of deep tendon reflex).²⁹

Late: Collapse of the oropharyngeal airway can occur when those muscles become weak. Two other late features are loss of the gag reflex, and pupil dilatation (possibly fixed). Skeletal muscles may be paralyzed with accompanying loss of DTR. A grave danger is the weakening of the diaphragm and accessory muscles; this can lead to cyanosis and/or CO₂ narcosis secondary to CO₂ retention. Overt respiratory failure can occur within 24 hours of symptom onset.⁶³
Classic presentations include anticholinergic features resulting from the impaired autonomic function: dry mouth, ileus, constipation, and urinary retention.²⁹

**Figure 10a, b** Mild botulism

In this 17 year old with a mild case of botulism, note in figure-a, the bilateral ptosis and mydriasis. In b, note asymmetric smile, disconjugate gaze.

**Table 7** CN findings seen with botulinum toxin

| mydriasis | diplopia | ptosis | photophobia | dysarthria | dysphonia | dysphagia |

Modified from ²⁹

Some or all will be present in any botulinum exposure.

Key negative findings include the patient being afebrile (unless there is a secondary infection), a lack of sensory nerve impairment, and the absence of mental status changes.⁶⁴ The paralyzing effects from botulism can last for weeks or months even with proper management (see section Treatment below).²⁹

The mortality related to botulinum toxin is secondary to paralysis of the respiratory muscles.⁶²
Labs

Routine laboratory studies and CSF show no abnormalities. 29

Microscopy

Since most laboratories do not have the appropriate tests for diagnosing botulism, the primary care physician should be prepared to send out samples including: serum (>30 mL), stool, gastric aspirate, and if possible: vomitus and suspect food. Ideally, collection should be done prior to antitoxin administration. However, if the patient is symptomatic, do not delay antitoxin treatment for the sake of sample collection (see section on Treatment, below). A current patient medication list should be sent with the samples. 29, 63

Radiographic findings

No distinctive radiological findings are associated with botulinum exposure.

Differential Diagnosis

The following illnesses may present with similar findings: Guillain-Barre, myasthenia gravis, or tick paralysis enteroviral myelitis (which would have CSF consistent with viral infection and usually an antecedent fever), Inflammatory myopathies (noted by elevated creatinine kinase), viral encephalitis, atropine poisoning (which demonstrates mental status changes), chemical nerve agents (marked by copious respiratory secretions and miotic pupils), staphylococcal enterotoxin B (SEB) (see table 8). Please note that only the bioweapons included in the differential diagnosis—nerve agents and SEB-- would be likely be seen in clusters. 29, 63, 64

Botulism can be distinguished from other causes of flaccid paralysis because in botulism, CN involvement is more prominent than weakness and flaccidity of the periphery; this is particularly true in the early stages. 29
Table 8 Differentiating botulinum, Chemical nerve agents, and SEB

<table>
<thead>
<tr>
<th>Features</th>
<th>Botulinum Toxin</th>
<th>Chemical Nerve Agents</th>
<th>SEB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset</td>
<td>12-24 hours</td>
<td>Minutes</td>
<td>1-6 hours</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Descending flaccid paralysis</td>
<td>Convulsions, fasciculations</td>
<td>Myalgia, headaches</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>No effect</td>
<td>Bradycardia</td>
<td>Mild elevation</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Early-normal, Late-paralysis</td>
<td>Dyspnea, Airway constriction</td>
<td>Cough-non productive, Chest pain</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Ileus</td>
<td>Painful diarrhea</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Ocular</td>
<td>Mydriasis, Ptosis</td>
<td>Miosis</td>
<td>Conjunctival injection</td>
</tr>
<tr>
<td>Salivary</td>
<td>Decreased</td>
<td>Copious</td>
<td>Slight increase</td>
</tr>
<tr>
<td>Death</td>
<td>2-3 days</td>
<td>Minutes</td>
<td>Rare</td>
</tr>
<tr>
<td>Response to Atropine</td>
<td>None</td>
<td>Improvement</td>
<td>Improves GI symptoms</td>
</tr>
</tbody>
</table>

Adapted from 63

Diagnosis

Presently, few laboratories have the capacity to test for botulinum toxins and therefore, there will likely be some delay in getting a definitive diagnosis. Supportive of the diagnosis would be an afebrile patient with no sensory impairment and no mental status changes who has flaccid paralysis with prominent cranial nerve involvement. The classic diagnostic features are summarized in table 9.

Table 9 Key diagnostic features of cutaneous anthrax

| 1. Clear sensorium-botulinum does not cross the blood brain barrier |
| 2. Afebrile |
| 3. Paralysis-symmetric, descending, flaccid. Cranial involvement is always present most commonly with one or more of the 4Ds of CN palsies: |
| Diplopia |
| Dysarthria |
| Dysphonia |
| Dysphagia |

Adapted from 29

The 1,2,3,4 of botulinum diagnosis
As always, distinguishing natural occurrences from a bioterrorist attack will be difficult but any case requires making such a distinction, when possible. Detecting an outbreak would require a thorough history, in addition to the bioterror history (see table 19), botulinum necessitates that dietary behaviors and history be sorted out. Inquiring about foods recently eaten to consider likely sources, others who may have similar if any (which is significant), is important. Beyond that, it would be clustering of signs, symptoms and other findings that would be the strongest indicator of an attack. If no common dietary source can be detected, it might suggest an inhalational attack (See table 10). Also suggestive, is the identification of a toxin that is not one of the commonly occurring ones in foodborne cases: commonly toxins are A, B, and E (which comes from fresh or salt water fish). C, D, G are thought likely to be used in an aerosol attack. 29

Table 10. Features Suggesting a Deliberate Release of Botulinum Toxin

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>An outbreak of a large number of cases of acute flaccid paralysis with prominent cranial nerve involvement</td>
</tr>
<tr>
<td>Outbreak with an atypical botulinum toxin type (i.e., type C, D, F, or G, or type E toxin not acquired from an aquatic food)</td>
</tr>
<tr>
<td>Outbreak with a common geographic factor but without a common dietary exposure</td>
</tr>
<tr>
<td>Multiple concurrent outbreaks with no common source</td>
</tr>
</tbody>
</table>

As with all potential cases of biological agents a careful travel/activity and occupational history must be taken and when botulinum is being assessed, as thorough dietary history, should be taken. Establish clustering by asking patients if they know of other persons with similar symptoms, or by noting similar signs, symptoms and findings in others. Adapted from 29
Table 11 Key diagnostic features of Botulism

<table>
<thead>
<tr>
<th>Making the diagnosis of Botulism</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pattern identification: Multiple, concurrent cases of a symmetrical, descending progressive motor paralysis</td>
</tr>
<tr>
<td>• Presentation: Symmetrical, descending and progressive flaccid paralysis with cranial nerve palsy</td>
</tr>
<tr>
<td>• Findings: History, clinical presentation, and epidemiology determine diagnosis</td>
</tr>
</tbody>
</table>

Treatment

Treatment is a two-fold approach: antitoxin and supportive measures.

Botulinum antitoxin, available from the CDC, should be administered as early as possible because the neutralizing effect acts on circulating botulinum in patients whose symptoms are still progressing. It does not reverse symptoms that are already present.\(^{63}\) Antitoxin administration should not delayed for the sake of sample collection. Once the symptoms have reached a plateau there is no more botulinum in the bloodstream and, hence, the antitoxin offers no therapeutic value. In foodborne botulinum, in which the toxin is thought to be absorbed slowly and steadily by the intestinal mucosa, the antitoxin is thought to be most efficacious. Antitoxins' usefulness in the event of an aerosolized bioterrorist attack is uncertain, because antitoxin has never been tried on humans in cases of inhalational botulinum. However, animal studies suggest that if given before onset of symptoms, antitoxin is highly effective; if given after onset of symptoms, respiratory failure still results (See Appendix C for dosing schedule).\(^{63}\) With the recommended dose, the amount of neutralizing antibody provided far exceeds the toxin levels found in
naturally occurring botulism patients, so further administrations are not needed. A bioterrorist attack with botulinum may result in dramatically higher serum toxin levels; it may be warranted to check antitoxin neutralization by retesting serum for toxin after treatment. 29

Should antitoxin be unavailable or delivery delayed, and foodborne botulism is suspected, standard detoxification measures such as activated charcoal may be administered, however no data exists to indicate the efficacy. 12

Please note: trivalent antitoxin is available against toxin forms A, B and E, and therefore identifying the toxin type is important. Although A, B, and E are the most common naturally occurring forms, a different form may be used in biological attack. USAMRIID has developed a non-specific antitoxin that is available under Investigational New Drug (IND) status for use on all seven botulinum toxin forms. 63

For the most part, supportive measures can include the use of enteral or parenteral feedings, admission to the intensive care unit, and mechanical ventilation. 63 Any patient in whom botulism is suspected or who is diagnosed but is having progressing symptoms should be carefully monitored for progression to respiratory failure as well as for the loss of the gag reflex, swallowing integrity, inspiratory strength and vital capacity. Classically, 20 % of foodborne botulism patients require mechanical ventilation. A major concern is that an attack with botulinum toxin causing a large outbreak would saturate available support measures (ICU beds, ventilators, available staff, etc). 29

Please note, in the presence of a concomitant secondary infection, the use of aminoglycosides and clindamycin are contraindicated because of their tendency to exacerbate neuromuscular blockade. 29
Vaccine

Currently there is vaccine available from the CDC under IND status. It is a pentavalent toxoid, given in a series of four shots, that offers pre-exposure prophylaxis against types A, B, C, D, and E. Use is only suggested for those individuals and populations at high risk to inhalational botulinum. The use of a heptavalent toxoid vaccine for post-exposure prophylaxis has shown positive results in animal studies; no human studies have been done nor are any planned.63

No pre-exposure prophylaxis is available to the public and at this time no plans exist for such a plan.63

Infection Control

Botulinum is readily destroyed. A temperature of 85°C or higher for more than five minutes decontaminates food or beverages.62

Any clothes or skin that come in contact with botulinum toxin can simply be washed in soap and water. Objects or surfaces may be cleaned in 0.1% hypochlorite solution. Natural degradation occurs within 2 days.29

Primary care physicians and their staff need only standard precautions when dealing with botulinum exposure. Isolation is not required.29

Notification

Diagnosis of botulism is considered a medical emergency (regardless of the source) and public health notification must begin at the local and state levels. If bioterrorism is suspected then federal notification both of public health and law enforcement must be initiated (see discussion on notification below).
**Plague (Yersinia pestis)**

Yersinia pestis is non-motile, non-spore forming, gram-negative rod. Infection with Yersinia tends to take one of three forms: bubonic, primary septicemic and pneumonic with bubonic, historically, being by far the most common form. Classically, the disease is transmitted from infected rodents to humans by fleas residing on the rats. As a biological weapon, pneumonic plague is expected to be the predominant form.\(^65\)

**Background**

The first documented epidemic of Yersinia is known to have occurred in 561 AD. It began in Egypt and spread along trade routes killing upwards of 60% of the populations of Europe, North Africa, Southern and Central Asia. The second great Yersinia outbreak occurred in 1346 and killed roughly one third of the population of Europe—roughly 25 million people. Historians believe that it’s nickname, 'black death' was coined during this time—likely because of the gangrene commonly resulting in the acral areas.\(^66\)

In both pandemics, it is thought that the bacteria spread locally from infected rats (and their fleas) and from people (and their fleas). The disease spread more distally from ships carrying all three—people, rats, fleas—traveling to distant sites. The third pandemic occurred in 1855 beginning in China but eventually spreading worldwide.\(^10\) There continue to be intermittent outbreaks throughout the globe. Present day outbreaks remain isolated and better controlled primarily because of higher standards of living, improved sanitation and hygiene, and the availability of antibiotics.\(^10\)
Though modern day outbreaks are of limited scope, the use of plague as weapon could change that. As discussed earlier, the Japanese military demonstrated in WWII that it had the capacity to initiate outbreaks in various sites in China.\textsuperscript{11} It is well known that most of the world's existing biological weapons programs include work on developing Yersinia as an agent in aerosolized forms—thus eliminating the need for rats and fleas.\textsuperscript{67}

It was estimated in 1970 by the World Health Organization (WHO) that 50kg (110 lbs) of Yersinia sprayed over a city would infect 150,000 people killing roughly 40,000.\textsuperscript{10}

\textit{Weaponized Yersinia versus Zoonotic Yersinia}

As always, distinguishing a case of naturally occurring disease from a bioterrorist attack is not easy. Large numbers of cases would, of course, be suggestive of an outbreak, and the clinical form (see below) itself might suggest that the zoonotic form or a deliberate attack might be more likely. Important criteria to consider include cases in areas with no zoonotic source, infection in patients with no discernable risk factors (such as exposures), and infection in the in absence of recent documentation of rodent deaths.\textsuperscript{10}

The signs and symptoms of weaponized plague may demonstrate a wide range of presentation. Please note the distinctions discussed below. The primary care physician must be cogniscent of both zoonotic and weaponized forms and even with a reasonable suspicion of zoonotic transmission a positive diagnosis must raise the specter of bioterrorism as possible source.
Epidemiology

In the past 50 years there have been roughly 1700 cases of plague in the US. Over 1400 (14% mortality) were bubonic, more than 220 (22% mortality) were septicemic, with the remainder being pneumonic forms (57% mortality).\textsuperscript{66}

Means of transmission

Naturally occurring Plague transmits to humans from bites of infected fleas that typically derived their infection through having bitten infected rodents. Generally, such transmission results in the bubonic form of the plague. A small percentage, however, will develop a septicemic form referred to as primary septicemic plague. It is important to note that in neither of these two forms can humans transit to other humans. However, those infected with pneumonic form of the plague can spread the disease through aerosolized droplets.\textsuperscript{66}

Because the most likely means of transmission used in a biological attack would be the use of aerosols, there would be a far higher percentage of the pneumonic form than is seen naturally. However, the extent of the outbreak from an attack would be influenced by a number of variable including climatic conditions, as well as the amount and types of Yersinia strain used. It is even possible that an attack could come in the form of a deliberate infection of a natural animal vector such as infecting a rodent with Yersinia within a major city.\textsuperscript{67}

Pathogenesis

In zoonotic transmission, bites from fleas carrying the plague introduce upwards of a thousand organisms into the dermis. Once present in the cutaneous tissues, Yersinia
will make its way through the lymphatics to regional lymph nodes, where despite being taken up by macrophages, they are able to survive and undergo rapid proliferation resulting in lymph node necrosis and destruction. Following the lymph node insult, bacteremia follows and potentially septicemia and shock.¹⁰

**Signs and symptoms**

Bubonic Plague-Classically, the presentation of symptoms from the bubonic form of plague between 2-7 days after receiving the fleabite. Clinical features include sudden onset of fever, headache, chills, and malaise; additionally, hepatomegaly and/or splenomegaly may be present. The pathognomonic feature is the formation of one or more buboes—one or more painful, erythematous, warm, swollen lymph nodes usually 10 centimeters or less in size that feels firm though the area around the bubo is edematous. Buboes are most commonly seen in the axilla, the groin, or cervical region (See figure 11). The pain from the bubo can be so intense that the patient may have limited in movement in that area.

**Figure 11** inguinal bubo

![Image of bubo](image.png)

Courtesy of CDC

Patient with characteristic buboes seen in the bubonic form of the plague.
Patients may also experience ulcerations at the site of the fleabite. Septicemia is a possible progression of the bubonic form (see below for discussion of septicemia) and is referred to as secondary septicemia. Secondary septicemia occurs in approximately 25% of the bubonic patients although roughly 80% are found to be bacteremic. Untreated, bubonic plague has a mortality of approximately 60%, and under 5% if treated.\textsuperscript{10, 65, 66}

\textit{Primary Septicemia}

There are some who are bitten by fleas carrying Yersinia but in whom no bubo formation occurs. Instead, the patient presents with septicemia; such a scenario is classified as primary septicemia.\textsuperscript{68}

The septic picture seen in both primary and secondary is similar to that caused by any gram-negative infection. These signs and symptoms include high fever, rigors, malaise, hypotension, nausea, vomiting, and diarrhea, and too commonly, DIC.\textsuperscript{68} The distinctive features seen with plague septicemia include thrombosis formations in the acral vessels, resulting in necrosis and gangrene of those regions. Black necrotic appendages and more proximal purpuric lesions caused by endotoxemia are often present. Organisms can spread to the central nervous system, leading to meningitis characterized by meningismus and fever.\textsuperscript{66}

\textit{Pneumonic Plague}

The pneumonic form can occur as a result of progression of either the septicemic or bubonic form. When pneumonic plague develops as a progression from bubonic or septicemia it is referred to as secondary pneumonic plague. It results when hematogenous spread of Yersinia occurs and bacilli end up in the lung. Symptoms include those of severe bronchopneumonia, chest pain, dyspnea, cough, and hemoptysis.\textsuperscript{10}
Primary pneumonic plague occurs when the bacilli are inhaled directly into the respiratory system and similar signs and symptoms to those of secondary pneumonic plague result. It is believed that a bioterrorist attack involving plague would likely present as a primary pneumonic infection or possibly typhoidal. Like the other forms, the incubation period runs between one and six days. Fever occurs first with dyspnea and cough that may be productive of water or blood, and possibly purulent sputum. Pharyngitis may also be seen in these patients accompanied by cervical adenopathy. There are additional reports that primary pneumonic plague patients suffer from gastrointestinal distress including nausea, vomiting, pain, and diarrhea.\textsuperscript{10,68}

Historically, pneumonic plague epidemics have been infrequent, but when they did occur in the pre-antibiotic era, the mortality rates were 100\%, and, in the antibiotic era, if treatment is delayed more than 18 hours after onset of symptoms survival is thought to be highly unlikely.\textsuperscript{67}

Distinguishing primary plague from secondary can be difficult but the absence of buboes is highly suggestive of primary. Unfortunately, the most definitive way to distinguish is via pathological examination. Untreated, death from primary pneumonic plague is within 4-6 days after onset of symptoms. Death is usually secondary to respiratory failure, circulatory collapse, multi-organ failure, or DIC.\textsuperscript{10}

It is important to keep in mind that pneumonic plague, as with all these forms, may progress to a septic picture and the resultant complications of (DIC), purpura, or small vessel necrosis (leading to gangrene in the periphery), azotemia, and multi-organ failure, as discussed above (see Section on septicemia above).\textsuperscript{66}
Labs

Changes in laboratory values are rather non-specific. Leukocytosis of up to 20,000 WBCs may be seen with greater than 80% PMNS and toxic granulations, coagulopathies may be seen, as well as LFT elevations. 67

Microscopy

Yersinia is a lactose non-fermenter, urease negative and grows best on MacConkey or blood agar plates. Detection of growth takes approximately 48 hours and yield distinctively small cultures. There are no widely available diagnostic tests for Yersinia, though gram staining is useful in that it will at least identify the gram-negativity. A Wright, Giemsa, or Wayson stain will reveal the classic “safety pin appearance” of Yersinia (see Figures 12 and 13). 10

If plague is suspected, the lab should be notified, as appropriate techniques can be utilized for proper diagnosis and BSL-2 protocol needs to be initiated. In the past, Laboratory acquired plague infections have occurred through improper protocol.

Figure 12 plague-microscopy

Courtesy of Univ. of NM Dept of Pathology
Wayson's stain
Figure 13 plague-microscopy

Plague bacteria in blood smear. Note safety pin appearance.

Courtesy of the CDC

Wright Stain: note bipolar or “safety pin” staining of cells.

Radiographic findings

Chest radiographs are most useful in assessing the pneumonic form of the plague. In such cases, the common radiographic findings are consistent with those of bronchopneumonia. Bilateral infiltrates and/or consolidation are typical findings as well (see Figure 14).
Figure 14 Plague: chest X-ray

Courtesy of Inglesby TV

Chest X-ray of pneumonic plague. Note the presence of left lower and middle lobe infiltrates

Differential diagnosis

Acute Respiratory Distress Syndrome, Cat scratch disease, cellulites, necrotizing fasciitis, pneumonia, tick-born diseases, gas gangrene.66

Diagnosis

Whether zoonotic or an act of terrorism, plague infection is never an isolated event. Whether the patient is seen in the office without any other cases having been reported, or if the physician sees a disproportionate number of such cases, the physician must recognize the diagnosis as the start of the epidemic, and notification of local, state, and federal agencies must be initiated immediately (see discussion below on notification.67
Early diagnosis is essential and, as always, requires a high index of suspicion regardless of the source. Reports of sudden increases in pneumonia cases complicated by sepsis signals the likelihood of a bioterrorism attack.\textsuperscript{10} Patients who are otherwise healthy, without risk factors for pneumonia, presenting with acute onset dyspnea, fever, and hemoptysis is highly suggestive; even more so if more than one case presents. If this scenario is seen but there’s no hemoptysis, consider anthrax.\textsuperscript{66}

There are no widely available diagnostic tests for Yersinia. Gram-staining is useful in that it will at least identify the gram-negativity. A Wright, Giemsa, or Wayson stain will reveal the safety pin appearance. Most zoonotic strains of plague produce an F1-antigen \textit{in vivo}, which can be detected in blood samples via immunoassay. A four-fold rise in antibody titer in patient serum is retrospectively diagnostic.\textsuperscript{67}

\textbf{Table 12} Key diagnostic features of Plague

\begin{tabular}{|l|}
\hline
\textit{Making the diagnosis of Plague} \\
\hline
\textbf{Pattern identification:} 1. Multiple, concurrent cases of fever, cough, chest pain, dyspnea; results in high morbidity and mortality. \\
2. Multiple, concurrent cases of gastrointestinal symptoms: diarrhea, nausea, vomiting, abdominal pain; results in high morbidity and mortality \\
\textbf{Symptoms:} Variable according to form of infection: cutaneous-cervical or inguinal bubo, gangrenous acral areas (late); respiratory-tachypnea, dyspnea, cyanosis, consolidations on chest exam; systemic-sepsis, shock, multi-organ system failure. \\
\textbf{Findings:} -Variable according to form of infection: -Chest X-Ray-consolidations, infiltrates, -Microscopy-bipolar or “safety pin” appearance of gram-negative bacilli. \\
\hline
\end{tabular}

Adapted from Inglesby\textsuperscript{19}
Treatment

No clinical trials have been done on therapeutic efficacy for plague infection so current recommendations are presumptive. However, current recommendations include initiating antibiotic therapy as soon as possible, selecting from among: streptomycin, gentamicin, ciprofloxacin, or doxycycline with a 10 to 14 day course. Symptoms improve within 3-4 days but the extended regimen prevents relapse. Chloramphenicol is the drug of choice for plague meningitis. Standard supportive therapies should be initiated, as is clinically warranted.\textsuperscript{10, 67}

Buboes will resolve with antibiotic therapy and generally require little in the way of specific management. Incision and drainage may increase risk of transmission, but may be performed with aspiration for symptomatic relief.\textsuperscript{66}

For persons with known exposure but who are asymptomatic, doxycycline should be given orally for one week or for the duration of exposure plus one week. Tetracycline or ciprofloxacin may be substituted (see Appendix C for dosing schedules).\textsuperscript{67}

Vaccine

At the present time, no vaccine exists that affects pneumonic plague, however active research and development is currently underway.\textsuperscript{10}

Infection Control

There is little data concerning person-to-person transmission so recommendations are of uncertain appropriateness. At this time, Standard Precautions are recommended. It is suspected that transmission can occur via droplet nuclei and thus wearing surgical masks is adequate protection along with strict patient isolation until the patient has been on antibiotics for at least 48 hours or until cultures come back.\textsuperscript{67}
There is no available data to suggest that decontamination is needed, as Yersinia is highly fragile lasting only a short time outside of a host. What’s more, with Yersinia, no spore form exists so ambient conditions do not permit prolonged survival.\textsuperscript{10}

\textbf{Tularemia (Francisella tularensis)}

Francisella tularensis, the causative agent of Tularemia, is a small, non-motile, facultative aerobic, intracellular gram-negative coccobacilli. Francisella \textit{tularensis} has three different species of which \textit{F. tularensis} biovar \textit{tularensis} is the most virulent form and it is the one most commonly seen in the US. The organism is considered to be one of the most infectious bacterial pathogens known. It is also quite hardy, able to persist for several weeks in water, soil, vegetation, or animal carcasses.\textsuperscript{70} Natural reservoirs include, mice, rats, and squirrels that attain the infection through direct contact and by insect vectors such as ticks and mosquitoes.\textsuperscript{72}

\textit{Background}

Tularemia was first identified in 1911 by a scientist investigating a suspected outbreak of bubonic plague in Tularane County, California. The disease has numerous modes of transmission and numerous forms of presentation.\textsuperscript{70} Waterborne epidemics were seen in Europe and the Soviet Union in and around WWII. It has been suggested that the Soviet outbreak, which occurred at the Russian front during WW II, was a result of a deliberate biological attack by the Russians. As discussed earlier, tularemia has been a foremost agent in the development of biological weapons since the 1930s. In 1969, the WHO estimated that 10 kg (20 lbs) of aerosolized \textit{F. tularensis} could infect 50,000 people and kill approximately 4,000. However, these numbers may be sorely outdated, particularly
since it is thought by some experts that during the 1980 and 90s, the Soviets were able to develop strains of *F. tularensis* that are resistant to antibiotics and vaccines.\(^7^1\)

**Epidemiology**

*F. tularensis* is found worldwide, though global incidence is not known. In the US, tularemia has been seen in all states except Hawaii but it is seen predominantly in the rural areas of southern, southwestern, and midwestern states. Since the 1990s, there have been less than 200 cases reported per year in the US.\(^7^0,7^1\) Cases are seen within a bimodal distribution: summer/fall, the larger of the modes, is thought to be secondary to tick transmission, and fall/winter is thought to coincide with hunting and trapping seasons. Most cases are secondary to direct contact of some kind although there are infrequent cases of infection from inhalation.\(^7^2\)

No significant differences in infection patterns are seen by age or by gender.\(^7^1\)

Overall mortality rates prior to the advent of antibiotics ran between 5 and 15%, and for pneumonic forms between 30 and 60%. In the antibiotic era, overall mortality runs at less than 2%.\(^7^1\)

**Means of transmission**

In the United States, most human disease is acquired through tick-borne transmission.\(^7^0\) Since infection can occur through bacterial contact with skin, mucosal linings, gastrointestinal epithelium, and the respiratory tract, humans can become infected by being bitten by infected ticks, by handling contaminated animals or animal products, by ingesting contaminated food or water, or by inhalation of aerosolized bacteria.\(^7^2\)

There is no person-to-person transmission with *F. tularensis*.\(^7^0\)
Weaponized *F. tularensis* could be dispersed in a variety of ways, with the greatest public health threat being from the aerosolized form. Aerosol dispersion in a densely populated area would likely result in widespread reports of fevers and non-specific symptoms within five days of dispersion. A large percentage of these people would develop pleuritis and/or pneumonitis. The abrupt onset of these symptoms in such large numbers and in otherwise healthy subpopulations should alert physicians and public health officials to the likelihood of an attack.\(^72\)

*Pathogenesis*

The virulence factors utilized by *F. tularensis* are not well known. Once inoculation occurs, regardless of the site, an intense focal inflammatory response occurs. PMNs and other leukocytes soon track in and a suppurative necrosis results with granulomas eventually forming. Pathology of the site shows a non-caseating, centrally necrotic region enclosed by epitheliod cells and multinucleated giant cells as well as fibroblasts in an array consistent with granulomatous pathology. *F. tularensis* is able to survive oxidative attacks by polymorphonuclear (PMN) cells, and the bacteria is taken up by macrophages and brought to regional lymph nodes at which time the bacteria multiplies and then spreads to organs such as the kidneys spleen, liver, lymph nodes, and lungs. Bacteremia can be detected early in the infection.\(^71\)

In primate studies of inhalational tularemia, peribronchial inflammation as well as in alveolar septal inflammation was observed within 72 hours of infection; later, pneumonia developed with consolidation, granulomas, and ultimately chronic interstitial fibrosis.\(^72\)
Signs and symptoms

Classically, following an incubation period of anywhere between 2 to 20 days (with an average of 3-5 days), a non-specific set symptoms begins with abruptly: fevers, chills, prostration, coryza, myalgias, dry cough, and headache. No hemoptyis, pleuric pain, or dyspnea is noted. Symptoms such as nausea, vomiting, and diarrhea may be seen. As the illness progresses, anorexia, weight loss, and sweats will be present additionally. If left untreated, these symptoms may continue for up to 4 weeks or possibly longer.\textsuperscript{73}

Six distinct clinical syndromes have been described, but these can exist as a continuum as well and more than one syndrome can present from the same infection. The type of clinical syndrome often relates to the mode of transmission by which the infection was acquired and to the portal of entry of infection. The six clinical syndromes are:

1. Ulceroglandular- (80\% of cases). This is the most common form and is seen when the means of transmission is from bites of infected ticks or animals, or direct contact with infected carcasses. Symptoms begin with fever and a solitary papular lesion (usually at the site of contact) that becomes centrally necrotic and tender within a few days and me be covered with an eschar; regional lymphadenopathy may be noted several days after the papule appears (See figure 15).

Figure 15 Tularemia: ulcer

![Tularemia: ulcer](image)

Courtesy of CDC
Thumb ulcer
Despite initiation of antibiotic therapy, the lymph nodes may become progressively more fluctuant and even rupture. Pneumonia develops in 10-15% of patients (see below for discussion of pneumonic tularemia).

2. **Glandular-** (10% of cases) This form (considered by some to be a subset of ulceroglandular) presents with one or more enlarged regional lymph nodes but without any cutaneous lesions or ulcerations (see figure 16).

3. **Typhoidal, -** (10%) generally occurring after an inhalational exposure (though it can occur from skin or mucosal contact), patients present with fever and chills but without any clear focus of infection. Patients may develop rhabdomyolysis and subsequent renal failure, sepsis and DIC (even with apparently negative blood cultures). Pneumonia may develop, as well, and can be quite severe. Pneumonia can occur in all the forms but is most commonly seen as part of typhoidal tularemia (see below for discussion of pneumonic tularemia).

The typhoidal form is distinctive in that, unlike the other forms, no lymphadenopathy is present.

In the event of a deliberate attack using aerosolized F. tularensis, typhoidal tularemia would likely be a dominant form. Untreated, typhoidal tularemia has a mortality of roughly 35%.

4. **Pneumonic –** occurring rarely in nature, the primary form results from inhalation of F. tularensis. It is seen mostly in laboratory workers while the secondary form, from hematogenous spread of an existing infection, is more common, otherwise. Pneumonic tularemia has a high mortality rate regardless of the source.

Symptoms include at least one of the following: pharyngitis, bronchiolitis,
pleuropneumonitis, and hilar lymphadenitis. If the pneumonia is secondary to hematogenous spread, then these symptoms are superimposed on the preexisting systemic symptoms. Even if the pneumonia is from inhalational exposure, it may be mild, sometimes overshadowed by the systemic symptoms. On the other hand, inhalational exposure may cause typhoidal symptoms without any major respiratory symptoms. It is important to note that the aggressiveness of the pneumonic process is highly variable sometimes leading to respiratory failure while other times not even developing into full-fledged pneumonia.\textsuperscript{71}

Since aerosol distribution is the probable form of a biological attack, it is important to be familiar with the pneumonic form in particular.

5. Oropharyngeal (less than 5% of cases)-ingestion of contaminated tissue or water and possibly through inhalation of aerosols are the means of infection in this form. The presentation is marked by exudative pharyngitis and sometimes oropharyngeal ulcerations. Stomatitis may also be seen. Impressive cervical and/or retropharyngeal lymphadenopathy may noted on exam (see figure 16)

Diagnosis is sometimes made after treatment for more routine pharyngitis fails.\textsuperscript{70-2}

**Figure 16** Tularemia: pharyngeal

![Image of pharyngeal tularemia](https://example.com/image)

*Courtesy WHO*

Pharyngeal tularemia: note the anterior cervical lymphadenitis. The lymph gland is swollen and fluctuant.
6. Oculoglandular- (less than 1% of cases). This form results from ocular contact with *F. tularensis*. Unilateral, painful, purulent or ulcerating conjunctivitis are the presenting symptoms. Other findings include preauricular lymph node enlargement and often with periorbital edema.\(^{72, 73}\)

Regardless of the form, infection may spread hematogenously, leading to secondary pleuropneumonia, septicemia, and possibly, meningitis. Tularemia sepsis is of particular concern and often fatal. The tularemia septic picture includes fever, diarrhea, vomiting, and abdominal pain. With progression, mental status changes are noted and coma may occur. Shock and systemic inflammatory response syndrome can occur with DIC, ARDS, and multi system organ failure.\(^{71}\)

*Labs*

Findings are generally non-specific. WBCs can be normal or up to 22,000 cells per milliliter. Other blood work is generally normal, especially early on. Up to 50% of patients may have mildly elevated transaminases, alkaline phosphatase, and lactate dehydrogenase. There may be evidence of creatinine kinase elevation as a result of rhabdomyolysis.\(^{20, 21}\)

*Microscopy*

Microscopy reveals a small bacteria, 0.2 x 0.2-0.7 microns (far smaller than anthrax) that is pleomorphic, with faint staining. Unlike Yersinia, it has no bipolar staining features. It is a fastidious organism with relatively slow growth, and most strains require special nutritionally supplemented media for growth.\(^{70}\)

At present there is no readily available rapid diagnostic laboratory test for *F. tularensis*. Routine microbiological screens would likely fail to pick up an otherwise
unlooked for case. If a case is suspected, the lab should be notified so special screens as well as precautions can be prepared. Samples should include respiratory secretions and blood (see Appendix D).

Diagnosis is made fluorescent antibody labeling performed only at designated public health labs, which can have results back within several hours.

Definitive diagnosis is made with cultures grown from pharyngeal, sputum, or even gastric aspirate samples; it is unusual for the bacteria to from blood samples. 

Radiographic findings

The first finding likely to be seen on chest X-Ray in the pneumonic form is bronchial infiltrates which later are seen as bronchopneumonic infiltrate involving at least one lobe. Pleural effusions may also be seen with hilar adenopathy (see figure 17). 

The typhoidal form would likely reveal mediastinal lymphadenopathy or pneumonia. 21.
Regardless of the form, 50% will have signs of pneumonia, and about 15% will have pleural effusions on chest X-ray (See figure 17). The pneumonic form may have other findings such as: Interstitial patterns, cavitary lesions, bronchopleural fistulae, and calcifications.

**Differential Diagnosis**

The broad and non-specific nature of the symptoms results in a large differential. The likelihood of tularemia can be assessed with a thorough exposure and travel history. Pneumonic- plague, anthrax (both of which would progress faster and have higher fatalities than tularemia), Q-fever.

Typhoidal- salmonella, rickettsia, malaria and other “typhoidal” illnesses.

Glandular- mycobacterial infection, cat-scratch disease (*Bartonella* infection), lymphogranuloma venereum, streptococcal or staphylococcal lymphadenitis, malignancy or lymphoma, fungal infection, and plague.
Diagnosis

In recent decades, tularemia has become so rare that it has warranted almost no diagnostic suspicion, however, the political climate is such that it must be given more of a priority. As with several of the other forms of tularemia, the accurate diagnosis is reached if an appropriate exposure history is elicited.\textsuperscript{70} As with all the category A agents, clustering and monitoring of signs, symptoms and other findings, and epidemiology will be the most powerful tool for noting an outbreak. Even in index case, a clinician may pick up the diagnosis if he or she notes the atypical pneumonia with Chest X-ray showing pleuritis and hilar lymphadenopathy as distinctive findings particularly if seen in more than one patient, and if the history supports the exposure likelihood.\textsuperscript{73}

Table 13 Key diagnostic features of Tularemia

### Making the diagnosis of Tularemia

- **Pattern identification:** Multiple, concurrent cases of severe respiratory, febrile illness
- **Presentation:** Early-febrile illness, otherwise, variable according to form of infection:
  - Pharyngitis, pneumonitis: cutaneous-ulcerations; lymphadenitis; late-sepsis, SIRS, inguinal bubo, gangrenous acral areas
  - Respiratory-tachypnea, dyspnea, cyanosis, consolidations on chest exam; systemic-sepsis, shock, multi-organ system failure.

- **Findings:** Variable according to form of infection:
  - Chest X-Ray-bronchopneumonic findings in at least one lobe, pleural effusion. Less common: diffuse granulomatous lesions, discrete infiltrates, enlarged hilar lymphnodes.
  - Microscopy-small, gram-negative coccobacilli in respiratory secretions.

Adapted from Dennis\textsuperscript{71}
**Treatment**

Outside the context of an epidemic, so that the primary care physician is managing just an individual patient, the recommended treatment is parenteral streptomycin or, alternatively, gentamicin (see Appendix C-Tularemia for dosing schedule). Tetracycline and chloramphenicol are also used but studies indicate higher rates of treatment failure and of relapse, probably because of their bacteriostatic mechanism. Fluoroquinolones appear to show good efficacy, with ciprofloxacin performs well in vitro, however its use in tularemia is not FDA approved. Macrolides and beta lactams show little effect against *F. tularensis* and should be avoided.  

Parenteral administration can be switched to oral when clinical improvement is seen. In large-scale outbreaks, oral administration is the rule. Doxycycline and ciprofloxacin are the preferred antibiotics (see Appendix C-Tularemia for dosing schedule).  

As was mentioned, there is a possibility that an attack may involve a modified strain of *F. tularensis* that is resistant to antibiotic therapy. Clearly, susceptibility testing will be done should an outbreak occur.  

**Vaccination**

Pre-exposure prophylaxis-There is a vaccine that had been available to those working with and around *F. tularensis* and was available under IND protocol; at present, however, the FDA is assessing it. Small retrospective studies of these workers (workers at USAMRIID) showed that the vaccine offered significant protection against
inhalational tularemia, and though there was little change in ulceroglandular rates disease course was less severe. Current recommendations are that the general public not be vaccinated. 73

Post-exposure prophylaxis—because the vaccine takes two weeks to offer protection, no recommendations exist for use of the vaccine after exposure. Studies have shown that antibiotic therapy started within 24 hours of exposure and continued for full course (see Appendix C-tularemia dosing schedule) offered full protection against inhalational tularemia. If more than 24 hours has passed since exposure, fever monitoring should be done and any inexplicable fever or prodromal symptoms within the next two weeks should be treated. 71

Close contacts of infected patients need not be treated, as person-to-person transmission is not known to occur. 73

*Infection Control*

Because no person-to-person transmission is known to occur, patient isolation need not be used, although standard precautions should be the practice.

As mentioned, F. tularensis is quite hardy. The extent of the hardiness, especially in a deliberate aerosol attack is unclear, but secondary dispersal is not a concern.

Contaminated surfaces and objects, applying 10% chlorine bleach (one part household chlorine for nine parts water) for 10 minutes is needed for proper decontamination. A 70% alcohol solution can then be used to for additional disinfection and for bleach removal.

Individuals with direct contact with contaminated fluid or objects should wash the appropriate body parts and/or clothes in soap and water. 70-73
Viral Agents

Viruses represent a very different type of biological weapon. In some ways they are much more dangerous. Significantly smaller than bacteria, viruses function by making their way inside of cells where they subsequently exploit cellular apparatuses and resources to replicate. Studying viruses is more complicated, more time consuming, and quite expensive. Antiviral medicines tend to be much less effective against viral infections as compared to antibiotic used for bacterial infections. There are two major types of viruses among the Category A agents: smallpox, and viral hemorrhagic fevers.

Smallpox (variola major)

Smallpox is a result of infection with the Variola virus, of the genus Orthopox, and contains double-stranded DNA virus.

Background

In what is arguably one of the finest public health achievement of the twentieth century, a virus that had killed more people than any other pathogen in the history of mankind, was confined to two specially selected labs. In 1980, smallpox was declared eradicated thanks to global vaccinations programs. At that time, it was declared that nations need not continue vaccination programs. However, it was not quite accurate to claim the virus was eradicated since, at the time of the pronouncement, the WHO approved two sites to maintain smallpox: the Centers for Disease Control and Prevention in Atlanta and the Institute for Viral Preparations in Moscow. The Soviets, apparently, did more than simple storage. They took the opportunity to undertake a large-scale
program to develop enormous quantities and, it is thought, resistant strains, of the virus to be fitted to intercontinental ballistic missiles and bombs. When the WHO called for both sites to destroy the stored virus in 1999, neither the US nor the Russians complied. The call was again ignored in June of 2002. Russia continues to maintain smallpox research and active development of strains with greater resistance to standard vaccines.

There are four considerations that make an outbreak more likely to spread quickly now than one would have 35 years ago. In the current population, there is essentially no immunity to smallpox because the disease is simply not occurring and vaccinations are no longer present. Secondly, because of provider unfamiliarity with smallpox, there will likely be a delay in smallpox recognition by care providers–thus a delay in implementing isolation, vaccinations, and more time for the disease to be transmitted. The population is more mobile than it was before both nationally and internationally. Finally, the world, the cities, the living conditions are universally more crowded.

There are two recognized forms of smallpox: variola major and minor. Variola Major is a more virulent strain with mortality rates roughly 30% or higher in a vaccine naïve population. Variola major has historically been more prevalent. Variola minor is considered rather mild with mortality less than one percent. Historically, smallpox, like its close relative chickenpox, followed seasonal patterns of outbreaks, peaking in the late winter and early spring. Such a pattern is likely secondary to the sensitivity of the aerosol droplets to higher temperatures and humidity. It is not known what sensitivities (or lack thereof) weaponized forms might have.

As a weapon, variola major is extremely dangerous. It spreads from person-to-person and vaccinations have been discontinued since 1972. Means of introducing a
smallpox infection for use in an attack are varied. The virus may be converted into an aerosolized form and released, it may be introduced via the use of fomites brought to high traffic areas such as cities or airports, or in the form of infected terrorist volunteers riding the subways and buses of major cities.8

Pathogenesis

When the virus lands in the host’s oropharynx the virus makes it’s way inside the mucosal lining. From there, it is taken up by macrophages and transported to regional lymph glands where the virus subsequently multiplies. Cytotoxic T cells and B cells are then activated. Antibodies begin to form within the first week of infection.79 On or about day four, the host becomes viremic while remaining asymptomatic. The virus continues to multiply at reticuloendothelial sites such as the spleen, bone marrow and lymph nodes. By day eight, a second viremic episode occurs, only this time the patient develops a viral syndrome with fever and malaise. As the immune response occurs, the virus is taken up by white blood cells and as it is transported through the small vessels of the dermis and pharyngeal mucosa, it is able to infect the surrounding tissue by approximately day 14. The classic pitted scarring that is left when the scabs form is secondary to destruction of the sebaceous glands which then shrink and are replaced first with granulation tissues and then soon thereafter with scar tissue.78,80

The lesions in the oropharynx quickly ulcerate because the tissue there, unlike the dermis, lacks a stratum corneum. As a result of the oropharyngeal lesions ulcerating, the saliva contains an enormous amount of virus.
Other than the skin lesions and a hyperplastic response of reticulum cells, no other organ systems are affected. 78

**Means of transmission**

Patients are most infective from the onset of the rash until the first scab forms when infectivity drops precipitously. Once an individual is infected, the virus is spread secondarily via aerosolized oropharyngeal droplets. The saliva may be positive for virus even up to six days prior to lesion formation, however the patient is not infective until lesion formation occurs at which time the viral content of the saliva climbs even higher. Additionally, infection can also occur through contact with contaminated objects-clothes, bedding, surfaces, etc. The urine is also known to contain live virus. 78

Infectivity among those in contact with the primary case is estimated to be between 40 and 80%. 81

It is thought that if 50 people were initially infected from an attack, the number of people infected secondarily would be 2500 to 5000, increasing 50 to 100 fold with each successive generation. Such numbers are due in large part to the relatively long incubation period until the lesions appear at which time infectivity is high. However, the lesions will not likely be properly diagnosed for several days during which time the virus is being transmitted. Once the lesions look like the classic form, infectivity level has diminished (see Signs and Symptoms below). 78

**Signs and symptoms**

Symptoms generally begin at the end of the incubation period that generally runs between one and two weeks. At the end of this period, the patient experiences high fever
sometimes with mental status changes, malaise, exhaustion, headaches, and backache, and abdominal pain has also been reported.

A maculopapular rash will also appear within three days of prodromal onset and fever will be noted (though not as high as the fever prior to the lesions). The rash occurs on the oropharyngeal mucosa, on the face and forearms and then spreading towards the trunk and downward to the legs (see figures 18, 19 below). By the second day, the rash becomes vesicular and the over the course of the subsequent week becomes papular until by around the 8th day the rash begins to scab leaving the signature pitted scar. The rate of rash progression is slow compared to other rashes, and

**Figure 18** Smallpox: facial lesions

![Smallpox: facial lesions](image)

*Courtesy of the CDC*

Characteristic smallpox lesions with facial distribution

**Fig. 19** Smallpox: lower extremity

![Smallpox: lower extremity](image)

*Courtesy of the CDC*

Characteristic smallpox lesions with lower extremity distribution
Encephalitis sometimes occurs, but secondary infections are uncommon.\textsuperscript{78-80}

Death from smallpox infection usually occurs around the second week of infection and is typically a result of toxemia from deposition of immune-complex formations and hypotension.\textsuperscript{80}

There are two variations in presentation of variola major that can occur but comprises less than 10\% of all cases and can be difficult to identify. There is a hemorrhagic form for which gestation appears to be a risk factor. The prodromal symptoms are similar, but the skin begins to become a dull, dark erythema, with petechial lesions and frank bleeding into the skin and mucosa soon thereafter. Death occurs in virtually 100\% of cases by day six.\textsuperscript{79}

The “flat” type, the second variation of variola major, has the same prodromal symptoms, but the vesicles never form into papules. Instead, there is confluence of the vesicles that feels soft and is flattened. Hemorrhages may be seen. The lesions leave no scar after they eventually peel away, presuming the patient survives.\textsuperscript{78}

Variola minor presents with similar symptoms but of less intensity—the prodromal symptoms are less debilitating and the rash merely scattered. A similar presentation is seen in persons previously vaccinated.\textsuperscript{79}

\textit{Microscopy}

Collection of viral specimens is extremely important but must be done by someone properly vaccinated (even as recently as the same day) who is wearing protective attire: mask, gloves, and gown. To make an adequate collection pustule and/or vesicular fluids are required. This may necessitate manually opening a lesion with a
sterile instrument and then transferring the fluid directly or by soaking it up into sterile material and transported in water tight, vacuum-sealed container. Few available labs will have the BSL-4 status needed to analyze the specimen. Establishing a positive result for an orthovirus requires an electron microscope. Definitive determination can be made through viral culturing followed by polymerase chain reaction (PCR) techniques. However, the diagnosis of smallpox will most quickly and effectively be made using context of clinical findings and history. Of course, once an outbreak is identified samples need no longer be collected. 78-80

Radiographic Findings
There are no key radiographic findings associated with smallpox diagnosis.

Differential diagnosis
Varicella, disseminated herpes zoster, impetigo, erythema multiform, scabies, hand foot, and mouth disease. Hemorrhagic smallpox- acute leukemia, meningococcemia. 81

Diagnosis
Any diffuse vesicular or papular lesions must elicit a differential that includes smallpox. A careful and thorough history must be taken to assess the risk of possible exposure. It must be understood by the primary care physician that the first cases in attack will take up to 2 weeks before the signature skin lesions appear and that the prodromal symptoms are quite non-specific, underscoring once again the critical importance of taking a thorough and pointed history. 80

To complicate matters, even if the skin lesions are visible, they are easily mistaken for Chickenpox. Distinguishing smallpox from chickenpox is extremely
difficult so some distinguishing features are as follows (See table 14): Varicella tends to have lesions which are at varying stages of maturation with new lesions presenting over the course of several days, the lesions tend to be

Figure 20 Smallpox versus Chickenpox

![Image: Smallpox foot (top) vs. chickenpox foot (bottom). Note the comparative degree of plantar involvement. Courtesy of the WHO]

more superficial. These lesions tend to be found more concentrated on the trunk.

Variola lesions tend to be of uniform maturity, with the majority of lesions presenting in a one to two day span. The lesions tend to be harder and are palpable more deeply in the skin. They tend to be found in greater concentrations on the face and extremities.
Table 14. Differences between varicella and variola

<table>
<thead>
<tr>
<th>Feature</th>
<th>Chickenpox</th>
<th>Smallpox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrome</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Confluent lesions</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Palmar, plantar involvement</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Umbilicated lesion</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Distribution</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Initial Distribution</td>
<td>Centripetal (trunk)</td>
<td>Centrifugal (hands, face)</td>
</tr>
<tr>
<td>Stages of lesions</td>
<td>Various</td>
<td>Same</td>
</tr>
</tbody>
</table>

↑ = high probability of being present
↓ = low probability of being present

thorough history. The key distinguishing historical feature being the presence of a viral prodrome preceding the lesion eruption is consistent with smallpox.78, 79

Diagnosis of either the malignant form or hemorrhagic forms is extremely difficult.

Table 15 Key diagnostic of diagnosing smallpox

Making the diagnosis of Smallpox

• Pattern identification: Multiple, concurrent cases of a maculopapular rash
• Presentation: Maculopapular rash especially of the mouth, face and arms and legs that is preceded by a prodrome with high fever
• Findings: Clinical presentation and epidemiology determine diagnosis. Must differentiate findings from chickenpox (see table 14)

Adapted from Henderson78
Treatment

At present there is no chemotherapeutic agent available to treat smallpox. Medical management is strictly supportive. There is some evidence that Cidofavir, an antiretroviral medicine has been found in animal studies to have activity against orthopox viruses though no clinical evidence exists showing its effect on smallpox infection. Further investigations are underway. In the event of an outbreak, Cidofavir would be made available through either the CD or NIH.

Infection Control

If a diagnosis is made or even suspected isolation is necessary for that individual until the lesions scabs dry and fall off. Household members, all healthcare providers and medical staff must be vaccinated, as should any one who has been in direct contact. Contact risk is increased by face-to-face contact or cohabitation after the onset of fever. Secondary contacts need not be isolated since even if infected they are not considered to be a transmission risk until skin eruptions occur. However, secondary contacts should have their temperature taken each day and any fever greater than 101° F during a subsequent 17 day period would warrant inpatient isolation. Ideally, home isolation should be arranged for the patient particularly in light of the fact that admission to inpatient isolation would put hospital staff at risk and that only supportive measures exist for management.

Isolation will generally be done with the patient’s cooperation. However, if necessary, quarantine can be enforced by designated public health officials if the public health is deemed to be at risk.
CDC guidelines indicate that known and suspected cases as well as febrile known contacts be admitted to designated hospitals for isolation; while asymptomatic contacts can be isolated at home. The Working Group recommends inpatient isolation only for known cases and that febrile contacts be isolated at home until diagnosis is certain. The differing view is based on the fact that infectivity is primarily an issue only after the lesions appear, and secondly, that in the context of a widespread outbreak, the CDC guidelines are impractical.

**Prophylaxis**

In recent years, there has been the planning and initiation of a smallpox vaccine program. At the time of this writing, however, it has been put on hold. The smallpox vaccination plan has been a source of enormous debate, a topic beyond the scope of this paper, however there are some points that useful to discuss here.

The smallpox vaccine itself is a live attenuated vaccinia virus, a member of the same family as variola. It is administered intradermally usually in the upper arm with a bifurcated needle. 2-3 insertions in the deltoid area are made for primary vaccinees and 15 for secondary vaccines all in rapid succession within an area no greater than 5mm in diameter. Within 4 days a pruritic, erythematous bump will appear at the site that over the following three weeks, blisters, is purulent, then a scab forms which eventually falls away (See figure 21). The vaccine site and resultant scab should be kept covered, with any direct contact by others or self should be avoided. Thorough cleaning is indicated if contact is made. Old dressings should be discarded with care by placing them in well-sealed plastic bags.
While the smallpox vaccine will offer 95% protection against a typical strain of variola major, there are some risks involved. Common side effects include low-grade fever lasting as much as two weeks, regional adenopathy. Less common side effects include generalized vaccinia (240 out of a million primary vaccinations), eczema (91 in 25,000), post-vaccine encephalitis (10 in a million). Risk of death from vaccine is estimated at 1 in one million. This data is all derived from epidemiologic studies done on vaccinees during the 1960s. Treatment of adverse side effects is managed with vaccinia immunoglobulin (VIG) injection or given along with vaccination in patients at risk. Some evidence suggests that VIG may be of use in post-exposure prophylaxis as well.

Another issue of concern is transmission of vaccinia from the vaccinee to contacts, resulting in generalized vaccinia. Vaccinia shedding does occur from the vaccinee for up to three weeks. The overall risk appears to run about 3 in 100,000 vaccinees, and nearly all cases occurred in close contact secondary shared households, but these assessments are based on epidemiologic studies done in the 1960s. At greater risk of acquiring contact vaccinia are those with preexisting eczema as was seen in these same studies.

Contraindications to getting the vaccine are eczema, immunosuppression (from malignancy, immunosuppressive medicines, radiation, etc), immunodeficiency, having household contacts with any of the above, pregnancy, allergy to vaccine components (glycerin, polymixin B, streptomycin, tetracycline, neomycin, phenol). It is important to note that these are relative contraindications with the exception of severe immunodeficiency. What’s more, these contraindications are in relation to pre-exposure
prophylaxis; there are no absolute contraindications for post-exposure prophylaxis if infection is certain.\textsuperscript{80}

\textbf{Figure 21} Smallpox: vaccination lesion

![Smallpox vaccination lesions](image)

Courtesy of the CDC
Lesion forming at smallpox vaccination site.

The vaccine was given routinely to one-year old children in the US until 1972. At present then, approximately 44 percent of the population is unvaccinated. The remaining population was vaccinated at least 30 years ago which means the protective affects of the vaccine is, at best, unclear. It is felt that ten years after single dose vaccination, the standard given to American children, antibody levels fall below quantities thought to be protective. A “modified,” or less severe disease course may be seen.\textsuperscript{78}

Vaccinations given at the time of a smallpox attack will offer protection or perhaps amelioration of signs and symptoms if administered up to 4 days after exposure. As mentioned, the Department of Health and Human Services plan to vaccinate “smallpox response teams” is presently suspended ostensibly out of concern for safety,
particularly after seven recent vaccinees experienced myocardial complications including 2 deaths. The plan had been to vaccinate those healthcare workers likely to be exposed to smallpox, such as select emergency room staff, first responders, and public health officials designated for fieldwork for such an event. As of April 4th, 2003 the total number of people vaccinated was 31,297. The HHS plan had anticipated vaccinating half a million health care and public health workers. In the event of a smallpox attack, any primary care provider and their staff who may be seeing infected patients should be vaccinated.

At this time there is no need for the general public to be given smallpox vaccine. There is no threat imminent and in the event of an attack, there is enough vaccine to administer to everyone and should the need arise the CDC plan would result in the vaccination of every American within days.

Smallpox and bioterrorism.

Among the Category A agents, all are found in naturally occurring settings albeit rarely. The only exception to that is smallpox. Thus, barring a truly extraordinary travel or occupational history, a case of smallpox indicates the use of a biological weapon and even a single case is deemed an international medical emergency. That is to say, diagnosing smallpox equates with diagnosing bioterrorism.
Viral hemorrhagic fevers (VHFs)

The VHFs are illnesses that result from four families of RNA viruses, all possessing lipid envelope, and causing hemorrhagic fever syndromes: Filoviridae which includes Ebola and Marburg viruses, Arenaviridae that include the etiologic agents of Argentine, Bolivian, and Venezuelan hemorrhagic fevers, Machupo and Lassa fever, Bunyaviridae that includes the Congo-Crimean hemorrhagic fever virus (CCHFV) and the Rift Valley fever (RVF), and finally, Flaviviridae which includes dengue and yellow fever viruses.89

Background

Since the first documented case of a Marburg in 1967, VHFs have been identified all over the world and have observable intermittent naturally occurring outbreaks. As a general rule, they reside in animal hosts (although the host of the Filoviruses is unknown).

It is documented that the VHFs have been weaponized by the US government as well as the Soviet, and later, Russian governments. Other governments are suspected to have done so as well.90

Epidemiology

There have been 18 Marburg or Ebola outbreaks of VHFs since 1967, mostly in Africa, with approximately 1600 patients. Most infection occurred through direct contact with infected animal or human fluid or tissue or by needle stick infection of health care workers. Percutaenous introduction of the viruses results in a higher mortality rate compared with other means of disease acquisition.89
Means of transmission

Soviet bioweapons scientists claim they aerosolized Marburg virus and found in primate studies that, as an aerosol, it is extraordinarily infectious. Further primate studies revealed that Ebola, Marburg, Lassa, and New World Arenaviruses can also cause infection through aerosolized forms.\textsuperscript{90}

Filoviridae (Ebola, Marburg)

Infection seems to result from indirect routes such as aerosol from infected animal feces, from infected arthropod bites, or by handling of infected animal carcass. Infected humans can infect others through close contacts.\textsuperscript{91} Precise information about the nature of transmission does not exist at present since outbreaks are sporadic, subside quickly, and tend to occur in areas without adequate public health involvement. Contact histories are often difficult to ascertain or are muddied. Person-to-person airborne transmission cannot be ruled out, though a number of these outbreaks have ended without airborne precautions ever being taken.\textsuperscript{90}

Ebola has been found in significant amounts in human skin and sweat glands and there is concern that casual contact could spread the virus.\textsuperscript{89} Primate studies indicate that the virus can be taken up through the mucosal lining.\textsuperscript{90}

Transmission does not appear to occur during the incubation (determined in primate studies to be several days).\textsuperscript{89,91}

Arenaviridae (Lassa, Machupo)

In the natural setting, Arenaviruses are transmitted to humans by the aerosols from infected rodent waste products or by contact of mucus membranes or open skin with the virus. Person-to-person transmission is believed to occur secondary to direct contact
with infected body fluid; transmission through airborne droplets cannot be ruled out.  

Bunyaviridae (RVF, CCHFV)

Humans become infected as a result of a bite from an infected mosquito, inhalation of aerosolized virions from infected animal, carcasses, physical contact with infected animal tissue, and there is also strong evidence that infection can occur through consumption of infected animal milk. It is presently felt that no person-person-transmission can occur despite the virus being found in oropharyngeal swabs.  

Flaviviridae (Yellow fever, Omsk hemorrhagic fever, and Kyanasur Forest Disease, Dengue)

Infection from this family is introduced into humans via bites: yellow fever and dengue from mosquitoes and Omsk HF and Kyanasur Forest disease from tick bites. No person-to-person bites have been reported.  

Pathogenesis

The basic pathophysiologic mechanism of how these viruses function in vivo is presently not fully understood. All the viruses appear to result in platelet deficiency and or platelet dysfunction, and all seem to lead to a bleeding diathesis. RVF and yellow fever tend to cause disseminated intravascular coagulation (DIC), while Marburg acts by causing direct endothelial and platelet damage and Ebola by cytokine dysregulation via a secreted glycoprotein.  

Filoviruses are able to necrose the visceral organ systems-especially the liver, spleen and kidneys. However, the mechanism of the necrosis is unclear; it may be secondary to damage of the local microvasculature or by cytotoxic effect of the filoviruses. As stated earlier, Marburg is believed to function by causing direct
endothelial and platelet damage while Ebola by cytokine dysregulation via a secreted glycoprotein.\textsuperscript{92}

Arenaviruses infection begins in the nasopharyngeal mucosa where it replicates and eventually is found in all tissue. Since little or no cytotoxic effect is noted, it is postulated that the virulence is a result of inducing cytokine dysregulation. The hemorrhaging seen with arenavirus infection appears to be secondary to both a secreted inhibitor of platelet aggregation and an induced thrombocytopenia. DIC tends not to be seen with Arenavirus infections.\textsuperscript{92}

Bunyaviridae infections, specifically RVF infections, have direct cytotoxic effects on the host cells. The mechanism for the bleeding diathesis is not understood but thought to be a combination of hepatocyte necrosis and vasculitis.\textsuperscript{90}

Flaviviridae, specifically yellow fever, has a direct cytotoxic effect on host cells (similarly to Raft Valley). Late in the illness, infection and subsequent destruction of hepatocytes occurs without an inflammatory component. RVF and yellow fever tend to cause DIC. The pathophysiology is unknown for Omsk HF and Kyanasur Forest disease but both involve destruction of the liver and spleen, and cause hemorrhagic pneumonia.\textsuperscript{90}

\textit{Signs and symptoms}

Current information regarding clinical presentations is based on reports from the naturally occurring epidemics. The range of signs and symptoms is quite broad and there are a significant number of patients who have presentations quite different than the textbook descriptions. What’s more, each particular virus has a greater or lesser tendency to present classically, making a definitive clinical diagnosis from among these difficult (See table 14 for distinguishing features).\textsuperscript{89,91}
Early: Following a 2 to 20 day incubation period, the classic VHF presenting symptoms include: a viral prodrome lasting less than one week with, headache, joint and muscle pain, nausea, abdominal pain, prostration, hypotension, bradycardia, tachypnea, conjunctivitis, pharyngitis, and non-bloody diarrhea. Rash is also a presenting sign but the nature of the rash varies among the viruses. RVF and the flaviviruses are accompanied by jaundice. $^{89,91}$

With filoviruses, RVF, and flavivirus the signs and symptoms come on rapidly while arenaviruses presents with slower onset. $^{89}$

Late: azotemia, oliguria, a worsening bleeding diathesis which may involve hematuria, hematemesis, petechiae, conjunctival hemorrhage, mucosal hemorrhage, DIC, and hypovolemic shock. A poor prognosis is suggested by the following CNS findings—delirium, convulsions, cerebellar deficits, or coma. $^{90}$

Long-term sequelae include alopecia, malaise, prostration, cachexia, diminished hearing and/or visual abilities, cerebellar dysfunction, pericarditis, and pancreatitis.

When shock, multi-organ system failure, and bleeding diathesis begin, death commonly follows.

Mortality rates run as low as 0.5% for Omsk HF and as high as 90% for Ebola. $^{89,9}$

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**Labs**

Laboratory abnormalities include: anemia or hemoconcentration, thrombocytopenia, elevated LFTS. A low WBC count is seen in nearly all the VHFs with the exception of Lassa that has an elevated WBC.
Coagulation studies reveal prolonged bleeding times, activated partial thromboplastin time, prothrombin time; elevated fibrin degradation products, and decreased fibrinogen.

Urinalysis may indicate proteinuria and/or hematuria.\textsuperscript{89, 91}

\textit{Microscopy}

No laboratories will be suited for diagnosing VHF's as BSL-4 is needed and only two labs in the nation could even accept samples in a suspected case. The only two sites that can accept specimens for analyses are the CDC and the USAMRIID. Plans exist to make making selected Public Health laboratories capable of handling such a sample but for the time being only these two exist.\textsuperscript{89}

However, should a sample be sent to one of these labs, diagnosis is made via antigen-capture enzyme-linked immunosorbent assay (ELISA), and/or by IgM antibody detection with antibody-capture ELISA, PCR, and viral isolation.\textsuperscript{17} Preliminary results can be given within 24 hours.\textsuperscript{90}

\textit{Radiographic findings}

No distinctive radiological findings are associated with botulinum exposure.

\textit{Differential Diagnosis}

Infectious diseases that could mimic VHF's include: Influenza virus, typhoid fever, viral hepatitis, non-typhoidal salmonellosis, leptospirosis, rickettsial infections, shigellosis, relapsing fever, and meningococcemia, and the infectious causes of DIC. Non-infectious diagnoses to consider include: fulminant hepatitis, leukemia, lupus erythematosus, hemolytic uremic syndrome, idiopathic or thrombotic thrombocytopenic purpura, and the non-infectious causes of DIC.\textsuperscript{89}
Diagnosis

As always, a high index of suspicion is needed to make the diagnosis particularly in the context of a potential bioterrorist attack. Because of the difficulty with obtaining laboratory diagnosis as discussed above, and because of the seriousness of VHF's because the rarity of seeing such a case in the US, the primary care physician must make a preliminary diagnosis based on the history and clinical presentation alone (See table 17). Further distinction of the specific VHF virus that is causing the infection will be even more difficult, but clinical clues may help differentiate these (see table 16)\textsuperscript{17-19}

Risk factors for a naturally occurring VHF infection include: travel history positive for recent visits to Africa and/or Asia, contact with sick animals or their corpses, sick human contact, recent tick bite (within 3 weeks). A deliberate infection with a biological agent would reveal no risk factors other than potential occupational and travel histories such as government officials or their employees, recent travel to monuments or political speeches, etc (see section Primary Care Physicians and Public Health below).

The WHO recommends making the diagnosis of an index if a series of clinical conditions are met (See table 17). Of course, in the event of an outbreak, the difficulty in making a diagnosis will be considerably less.\textsuperscript{90}
### Table 16 Clinical distinctions among Category A VHF

<table>
<thead>
<tr>
<th>Virus</th>
<th>Clinical findings</th>
<th>Incubation Time, days</th>
<th>Contagious?</th>
<th>Treatment</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filoviruses</td>
<td>Abrupt onset of high Fever, weakness. Generalized maculopapular rash &lt; day 5. Hemorrhaging and DIC are common.</td>
<td>2-21</td>
<td>Yes</td>
<td>Supportive</td>
<td>50-90%</td>
</tr>
<tr>
<td>Marburg</td>
<td>Abrupt onset of high fever, myalgias. Maculopapular rash of face, neck, trunk, and arms. Hemorrhaging and DIC are common</td>
<td>2-14</td>
<td>Yes</td>
<td>Supportive</td>
<td>25-70%</td>
</tr>
<tr>
<td>Arenaviruses</td>
<td>Gradual onset of fever, nausea, abdominal pain, exudative pharyngitis, cough, conjunctivitis, facial flushing, diffuse lymphadenopathy. Late: edema of head and neck, pleural and pericardial effusions. Hemorrhaging less common.</td>
<td>5-16</td>
<td>Yes</td>
<td>Supportive, ribavirin</td>
<td>15-20</td>
</tr>
<tr>
<td>Lassa Fever</td>
<td>Gradual onset of fever, nausea, abdominal pain, cough, conjunctivitis, facial flushing, diffuse lymphadenopathy. Hemorrhaging less common. petechiae possible. CNS involvement-dysarthria, fasciculations of tongue, local and generalized seizures.</td>
<td>7-14</td>
<td>Yes</td>
<td>Supportive, ribavirin</td>
<td>15-30%</td>
</tr>
<tr>
<td>New World Arenavirus</td>
<td>Gradual onset of fever, nausea, abdominal pain, cough, conjunctivitis, facial flushing, diffuse lymphadenopathy. Hemorrhaging less common. petechiae possible. CNS involvement-dysarthria, fasciculations of tongue, local and generalized seizures.</td>
<td>7-14</td>
<td>Yes</td>
<td>Supportive, ribavirin</td>
<td>15-30%</td>
</tr>
<tr>
<td>Bunyaviruses</td>
<td>Fever, headache, retro-orbital pain, photophobia, jaundice. Hemorrhaging rare. Retinitis in roughly 10% as late as 4 weeks from fever.</td>
<td>2-6</td>
<td>No</td>
<td>Supportive, ribavirin</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>RFV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flaviviruses</td>
<td>Fever, facial flushing, myalgias, conjunctival injection. Full remission occurs or a short remission followed by fever, bradycardia, jaundice, renal failure, and hemorrhaging.</td>
<td>3-6</td>
<td>No</td>
<td>Supportive</td>
<td>20%</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omsk HF</td>
<td>Fever, cough, conjunctivitis, papulovesicular lesions on oropharynx, facial and trunk flushing, diffuse lymphadenopathy, splenomegaly. Pneumonia and CNS involvement may occur.</td>
<td>2-9</td>
<td>No</td>
<td>Supportive</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Kyanusar Forest disease</td>
<td>Similar to Omsk, but biphasic. Phase 1: 6-11 days, then short remission: 9-21 days. &gt;50% relapse and develop meningoencephalitis.</td>
<td>2-9</td>
<td>No</td>
<td>Supportive</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

Adapted from Borio
Table 17 Criteria for diagnosis of VHF

<table>
<thead>
<tr>
<th>Making the diagnosis of VHFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pattern identification: Multiple, concurrent cases of febrile illness with evidence of bleeding diathesis</td>
</tr>
<tr>
<td>• Presentation: Febrile: 1. temperature 101°F of less than 3 weeks duration;</td>
</tr>
<tr>
<td>2. No risk factors for hemorrhagic manifestations;</td>
</tr>
<tr>
<td>3. Two or more of the following hemorrhagic symptoms:</td>
</tr>
<tr>
<td>hemorrhagic or purple rash,</td>
</tr>
<tr>
<td>epistaxis,</td>
</tr>
<tr>
<td>hematemesis,</td>
</tr>
<tr>
<td>hemoptysis,</td>
</tr>
<tr>
<td>hematachezia</td>
</tr>
<tr>
<td>no established alternative diagnosis.</td>
</tr>
<tr>
<td>Findings: History, presentation, and epidemiology determine the diagnosis</td>
</tr>
</tbody>
</table>

Adapted from Borio 90

On the whole, the medical management of the various VHF is the same regardless of which virus is actually the cause: supportive measures. Such measure will likely be needed to address the hematological, hemodynamic, neurological, and pulmonary issues. As the disease progresses, patients will likely need intensive fluid resuscitation, electrolyte management, dialysis, mechanical ventilation, as well as administration of pressors. Clearly, then, many will require placement in critical care units.91

Because of the associated bleeding diathesis, injections and anticoagulant medicines should be avoided, if possible.

It should be noted that the extent of fluid resuscitation in treatment of volume loss must be evaluated with consideration of pulmonary edema.89

There are no FDA approved antiviral medicines for treatment of VHF.
Ribavirin, the antiretroviral medicine, has been shown in animal studies to improve mortality in RVF, and both morbidity and mortality in Lassa fever. It is available under compassionate use protocols (see Appendix C for dosing schedule). 89

Bunyaviruses, specifically, RVF, seems to respond to alpha interferon in animal experiments, but only if administered just prior to or just after infection. The interferon seems to reduce viremia and minimize liver cytotoxicity. Passive immunization with neutralizing antibody inhibited viremia in infected primates. 90

Those with possible exposure should be monitored for fever (of 101 or greater) and other clinically suggestive signs (see table 17) for up to three weeks following exposure.

Prophylaxis

Pre-exposure: At the present time, vaccinations for VHF are being researched. The only licensed vaccine is for yellow fever.

Post exposure- There are no guidelines or even recommendations for management of post-exposure prophylaxis in an asymptomatic patient. If the patient begins to demonstrate the defining signs and symptoms (see table 17) ribavirin therapy should be initiated if VHF is presumed. However, if it is known to be a filovirus or flavivirus, ribavirin is not indicated. 90

Percutaenous and exposure with infected bodily fluids should be washed with soap and water while mucocutaneous exposures should be irrigated generously with saline. 89
Infection Control

Extreme caution should be practiced when evaluating and/or treating a patient thought to have VHF. All bodily fluids and secretions of VHF patients should be handled with extreme care. VHFs will have impressive viral loads in these fluids. Clearly then, sharps require the same level of vigilance. The filoviruses and arenaviruses may be transmitted through aerosol form and thus admission to an inpatient room with negative air pressure is warranted with contact isolation measures including double gloves, shoe coverings, full, impermeable gowns, and face shields. If patients are actively hemorrhaging, coughing, vomiting or having diarrhea, airborne isolation will be need.  

Patient Education

Many Americans are now quite concerned about the affect of world politics on day-to-day life in the United States, including the possibility and consequences of additional terrorist attacks. An attack involving biological or other weapons of mass destruction is implicit in that fear and is a popular topic in the mainstream media. As a result, it is likely that people will have concerns and questions about these issues. It stands to reason that primary care physicians will be looked to for answers by their patients. In every community, patients will likely come to their primary care physician at some point looking for health related (and possibly non-health related) answers. Much of the information provided in the preceding sections was included in anticipation of areas of patient inquiry. However, additional information may prove to be useful that was not mentioned above or has been re-worded here for purposes of addressing specific
questions. A list of freely available patient information resources on bioterrorism is included in Appendix H as well as freely available physician information resources in Appendix I.

Answers to common patient questions

Q: What is the likelihood of a large biological attack on the United States?
A: The risk of a large-scale attack is thought to be quite low, primarily because of the logistical complexity involved. Many experts consider the possibility unlikely at this time.

Q: I received a smallpox vaccine as a child and don't recall any problems with bad reactions. Has the vaccine changed?
A: There very similar problems today as there was previously but back then there was not the same level of attention in part because the risk of contracting the disease was overshadowed by the much unlikelier risk of side affects from the vaccine.

    Remember, while minor side effects are somewhat common, life-threatening side effects are uncommon.

    Historically, between 14 and 52 people per 1 million vaccinated experienced potentially life-threatening reactions. It is estimated that between 1 and 2 people out of every 1 million actually died as a result of life-threatening reactions to the vaccine.

Q: Can I contract smallpox from getting the vaccine?
A: No. The smallpox vaccine does not contain smallpox virus. However, the vaccine does contain another virus called vaccinia, which is related to smallpox. This virus is not dangerous but it is possible to develop an infection from vaccinia and also to transmit infection to anyone who might touch the vaccination site or anything that has come into contact with it (your hands, old bandages, etc). This can be prevented by keeping the vaccination site covered at all times, by proper maintenance of the vaccination site with clean dressings and proper disposal of old dressings, and hand washing.

Q: Is it possible to get vaccinia from someone who has recently been vaccinated?
Yes. Vaccinia is spread by touching a vaccination site before it has healed or by touching bandages or clothing that have become contaminated with live virus from the vaccination site. Vaccinia is not spread through airborne contagion. Symptoms of infection with vaccinia virus include rash, fever, and head and body aches.
Q: If I have received a smallpox vaccine, are my small children at home at risk?
A: No. There is no increased risk to children because of your vaccination. Additionally, the only way to infect a child in the household or anyone else is through contact with the vaccination site or contact with anything that has been in contact with the site such as clothing, bandages, etc.

Q: If I received a smallpox vaccine as a child, am I still protected?
A: It appears that childhood vaccination does not offer protection beyond 10 years. However it may offer some ameliorating benefit. See section on “smallpox vaccine” above. CDC

Q: If I received the smallpox vaccine as a child and did not have a bad reaction, does that mean I can get vaccinated now without a problem?
A: Having been vaccinated without adverse reactions as child does not ensure freedom from adverse vaccination reactions now. The risk factors for adverse reactions, such as eczema, might not have arisen at that time. Also, as an adult, other illnesses may be present that are undiagnosed (e.g., cancer, heart conditions, immunodeficiencies, etc) and that may increase your risk for an event. 87

Q: How do I best prepare for a bioterrorist attack?
A: Preparations should be no different than for natural threats (hurricanes, blizzards, etc). Keep a few days of food and water in storage as well a radio with fresh batteries, cell phone batteries, etc.

Another important item is a list of emergency contact numbers accessible at work, school and home. Items such as gas masks are not needed since they only work for certain agents and need to be properly fitted. Ready.gov

Q: Should I take antibiotics if there is a bioterrorist attack?
A: No. Antibiotics are not useful against all agents. Regardless of the agent involved, taking antibiotics improperly may cause you to become ill, and may make infection worse. Follow your doctor’s instructions for taking antibiotics. CDC

Q: What should I do if there is a bioterrorism attack?
A: According to FEMA, the best things to do are as follows: Listen to the radio or television for instructions and advisories. If you are to remain in the building where you are, turn of ventilation systems, air conditioners, etc. Try to keep a radio with you. Stay in the most internal room—that is, the room with fewest, or without windows.

If you are outdoors, stay as far from contaminated airways as possible, upwind if possible and listen to the radio for instructions.

Although only masks with proper filtration ability provide safety, covering your mouth with fabric thickly layered that still allows proper breathing—such as a folded shirt can be of some help. Wash yourself with soap and water when possible.

Q: Should I seal my windows and doors with tape in case of a biological attack?
A: While there is some disagreement about sealing windows and doors, most experts agree that sealing windows and doors probably won’t make enough of a difference to
warrant such action. It may slow down air movement, but it won’t stop it and thus probably won’t offer much protection. Additionally, if you are in a room with a fuel-based heater, carbon monoxide may build up.

**Q: What should I do if I see an unidentified white powder in a package or letter or anywhere else?**

**A:** Most importantly, do not touch it. If it is possible, keep it covered. Alert others in the vicinity of the concern. If you are at work, notify your supervisor and a law enforcement agency. Likewise, if you’re at home, call the local law enforcement agency. Wash your hands or exposed parts thoroughly with soap and water. Try and determine who may have been exposed to the powder, write down their names and give the list to the law enforcement agents.

**Q: What should I do if I think I am exposed to a biological agent?**

**A:** Call your doctor or go to the nearest ED if necessary. After evaluation, the doctors will decide if further work-up is needed or if public health officials need to be contacted.

**Q: In the event of a biological attack, is it OK to drink tap water?**

**A:** Unless instructed not to do so, it is safe to drink from the tap. Contaminating the water supply is extremely difficult because of the dilutional effect from the tremendous volume and because of the antiseptic nature of processing involved in water treatment.

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**Primary Care Physicians’ Issues in the Context of Bioterrorism**

It is worth repeating that bioterrorism presents a number of challenges for the primary care physician.

A community-based physician needs to be intimately familiar with the any bioterrorist preparedness and response plans that the local municipality is intending to use. Being familiar with national responses as well as those of FEMA and the CDC so that in the event of a diagnosis or simply living through an attack, as a physician you’ll know what proper protocol is.93

The primary care physician should have a readily available list of all necessary phone and fax numbers for health and law enforcement officials at the local, state, and
federal levels to be notified if he or she suspects diagnosis of an infection with a biological agent (see Appendix E).

Should a primary care physician suspect a case of infection with a biological agent, the process of notification must begin. Local health officials should be informed for assistance in making the determination but also for preparing to implement action should it turn out to be an attack immediately (see appendix H for phone and fax numbers of state and nationwide contact information). The Category A Biological agents fall into Category 1 reportable diseases in Connecticut, requiring immediate telephone notification of both the local and state health departments (see Appendix G) that day along with submission of a PD-23 Confidential Disease report (see Appendix H-1) to be mailed within 12 hours in an envelope marked “confidential.” All communications must include the physician’s name and address (and that of the person reporting if it is not the physician), as well as the name, address, race/ethnicity, sex, and occupation, gender and occupation of the person affected. If deliberate exposure is suspected, the FBI must be notified, as well (see table 18). ⁹⁴,⁹⁵

Table 18 Notification for infection with a biological weapon

<table>
<thead>
<tr>
<th>Notification (see Appendix E)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Local public health officer (See appendix H for phone and fax)</td>
<td></td>
</tr>
<tr>
<td>2. State Health Department : Epidemiologist and Bioterrorism coordinator (see Appendix G for phone and fax).</td>
<td></td>
</tr>
<tr>
<td>3. Center for Disease Control and Prevention (see Appendix G for phone)</td>
<td></td>
</tr>
<tr>
<td>4. FBI, if diagnosis, is probable (see Appendix G for phone)</td>
<td></td>
</tr>
</tbody>
</table>
The earliest possible identification, notification, diagnosis and treatment is vital not only for the patient but also for the community and possibly the nation. The primary care physician should be familiar enough with the biological agents to competently manage the situation until public health and law enforcement officials begin their fieldwork or longer if public health officials are unable to be contacted or response is delayed. Proper management of the situation by the physician includes not only medical management but also adequate quarantine, if appropriate, administration of prophylaxis as appropriate, etc (See above sections on category A agents, and Appendices A through G).

There are several ways to develop and maintain a strong working knowledge of biological agents, their symptoms diagnosis and management. Numerous medical books are available but David Henderson’s book, “Bioterrorism: Guidelines for Medical and Public Health Management” (published by JAMA, 2002) stands out among them. Other means include utilizing online resources such as those listed in Appendix I. One site, the Agency for Healthcare Research and Quality is designed specifically for primary care physicians and even provides quizzes to test bioterrorism knowledge. Both the US military and CDC offer regular bioterrorism related trainings, seminars--some live on satellite others available on video--- and CME credits may be gained for such trainings. The CDC provides trainings through its Health Alert Network that makes available previous broadcast and webcasts. The CDC also maintains updates and notifications through an email registry for clinicians. See Appendix I for further information.
The primary care physician must be ever vigilant. As has been discussed repeatedly here and elsewhere, the signs and symptoms of the biological agents are non-specific, especially early on. When a patient comes into the office with such symptoms, the possibility of biological agents cannot be dismissed out of hand. As with the establishment of any diagnosis, a good history is one of the best tools a clinician has. However, the history will have to be thorough, even pointed at times, in order to determine the likelihood of an exposure (See table 19). Areas to inquire about include:
Table 19 Bioterrorism History Taking

- Full HPI-including details about the onset, timing, rate of progression, and nature of signs and symptoms.
- Full PMH noting relevant co-morbidities or medicines-Full list of medicines the patient is on including any treatments taken to treat present symptoms, of note are antibiotic regimens.
- Full Social History- Member of high-risk, high profile group organizations. Including politicized, loved/hated- ethnic, racial, religious, political, activist groups, organizations, or associations.
- Occupational History-
  - A. High risk occupation-
    1. Governmental: postal worker, elected officials, government official, government employee, postal worker, FBI or other law enforcement agent. City, state or federal employees of any capacity (but particularly those with jobs in high risk departments).
    2. Non-governmental: Employed at major corporation (such as Wall Street firms, working for major media outlet-television, radio, newspaper.
    Low-profile job with high profile associations—mailroom worker at media company, fortune 500, government office.
    3. Related occupation-lab tech, researcher, healthcare.
  - B. Close association (spouse, parent, significant other) with any of the above
- Exposure history-
  - A. Animal-rodent or rabbit contacts, exotic animal or carcass contacts
  - B. Miscellaneous-contact-strange or suspicious packages, substances, liquids, receiving gifts or imported goods from foreign lands.
  - C. Sick contacts- close association with others with similar symptoms
  - D. Ingestion history
    1. Diet-any changes in eating habits, unusual foods, canned or jarred items, illness in others who ate same foods
    2. Water---unusual water sources (camping, swimming)
- Travel history:
  - A. International
    1. Developing nations or locales where naturally occurring infections of Category A, B, and C occur; visits to such countries plus contact with animals, or sick contact; countries with strong anti-American.
  - B. Domestic
    1. Recent visits to prominent sites-monuments, government buildings, tourist spots, (high ranking), attendance at political speeches or rallies; visits to major US cities-New York, Boston, San Francisco.
- Cluster history-illness associations- co-workers, family members, travel group, neighbors, fellow travelers.
  Clustering of animal deaths in local area or traveled to areas.

Bioterrorism History—This is by no means intended to be an exhaustive list but meant to guide the physician in taking a thorough history.
high-risk jobs, high-risk associations, sick contacts-human and animal; international
travel-for high-risk destinations both for infections or politics, likely target sites, etc.

The clinician should be prepared to collect adequate samples for laboratory study’
and should comfortable with how to properly and safely collect samples (See Appendix
D). Medical management will likely be needed. The primary care physician should be
familiar with the regimens as well as for the differences between treating an isolated case
versus treating patients amidst an epidemic—which centers on parenteral versus oral
administration (see Appendices C and B). Unfortunately, at the present time, no clinical
pathways exist to help the primary care physician with such distinction and thus the
physician is relying on history, empirical epidemiology, and clinical acumen to know
where bioterrorism sits in the differential diagnosis.

As a general rule, infection with biological agents will be extremely low perhaps
even last (or lower) on a differential diagnosis, but any positive findings from the history
will elevate it. Because a large-scale attack would affect large segments of the
population, epidemiology is useful is identifying the clustering of non-specific illnesses
and concurrent patients with similar signs, symptoms and other findings. As well as
concurrent cases with similar signs, symptoms and other findings. Certainly, if other
patients come in with similar histories such as attendance at a public event and similar
symptoms, especially unexplained fever or respiratory distress would be suggestive.
Ages, co-morbidities (or the lack thereof) may be useful as well as would, reports of any
recent animal deaths in the area. (See Table 19)
The primary care physician must be prepared to step outside the confines of clinician and into the broader role of public health provider. What’s more, since the presenting symptoms of a biological agent may not be specific enough for immediate diagnosis, the primary care physician must be prepared to follow-up on all the necessary issues should a positive diagnosis be confirmed. For example, by learning of an outbreak or of positive test results immediate notification not only of the proper public health channels must take place, but also following up with the patient as a top priority as well, and contacting other patients who may have presented with similar symptoms for advisement, possible isolation, further work up, initiation of medicines for the patient and prophylaxis for contacts, etc. Or if the primary care physician is suspicious, then the patient needs proper education about signs and symptoms to be on the watch for and to return to clinic or report to the nearest ED if necessary. The physician must always be mindful of appropriate prophylactic considerations for staff and for self.

Another issue that relates to living under the threat of bioterrorism is accurately ruling out the diagnosis infection with biological agents, especially for an Americans whose fear and anxiety levels are heightened since September 11th, and even more so with the present military presence in Afghanistan and Iraq. Sometimes referred to as the “worried well,” these patients are symptomatic but no physical problems can be detected. Since the post-September 11th anthrax attacks, every few months or so, suspicious white powder is found somewhere causing a furor and much anxiety. As recently as April 22, 2003, was the headline “Postal workers hospitalized in US Pacific Northwest after Biotoxin Found” referring to a Tacoma postal distribution center, while later the same day suspicious white powder was found at a cargo terminal in a Florida airport.
Hundreds of people were evacuated. The postal workers went through a precautionary
decontamination process, and one cargo worker complained of a burning sensation in his
nose.96 In the 18 months since the post-September 11th anthrax attacks, there are at least
six New York Times reported incidents involving “suspicious white powder” suspected
to be a biological agent. Fortunately, all have turned out to be non-toxic, two important
issues are raised: firstly, that although the immediacy of the post-September 11th anthrax
attacks may be gone, there is an underlying anxiety and vigilance that burns in the public
consciousness and is stoked by these intermittent powdery scares. In many of these cases,
‘patients’ were brought for medical evaluation. Some even reported symptoms. This
brings again the issue of managing the worried well. Prior to the assessments that
powders were benign, these patients were legitimately afraid for their health. This is a
reminder that the worried well patient is not to be written off as paranoid or neurotic but
that the concerns can be well-founded and that the state of the world makes such patients
a legitimate part of the primary care physician’s responsibility to take seriously and act
with understanding.

Clearly any serious diagnoses will need to be ruled out to the physician’s
satisfaction but the patient can be helped with some education on the subject of
bioterrorism, risks, agents, and other information, as well as empowered to seek out
information, create “emergency kits,” etc (see patient online resources Appendix H).97

Another important role for the primary care physician will be the monitoring of
those on prophylaxis for exposure, as was seen in the post-September 11th anthrax
attacks. Not only does the patient need to be monitored for possible delayed infection, but
for adverse reactions to the prophylaxis, as well. For the post September 11th anthrax
attack, the administration of prophylaxis was done through public health authorities but included local primary care physician acting in capacities such as ensuring informed consent, advising patients about their exposure risks, the pros and cons of vaccines and antibiotics, management of side effects, the further intricacies of prophylaxis while dealing with underlying chronic illnesses, drug interactions, etc.\textsuperscript{42} Even under the most peaceful and quiet of times, we have entered an era when infection with biological agents must be included on the applicable differential diagnoses no matter how low the likelihood seems.

The take home message for primary care physician then is that their role focuses on three main points:

1. Recognition/diagnosis of index and/or clusters of signs, symptoms and other findings
2. Prompt and proper medical management and infection control
3. Prompt contacting of local, state, federal public health authorities as well as law enforcement authorities, as needed.\textsuperscript{42}

It is also important to keep a larger perspective, as physicians naturally focus on the medical issues and hopefully on the public health issues as well. However, in the event of a bioterrorist attack, there are other, sometimes more pressing issues, and the physicians must adapt to the circumstance. In other words, if the primary care physician suspects that a patient is indeed infected with a biological agent, a scenario is elicited that is complex and unfamiliar. Such an infection would mean not only a serious illness, but also a crime, an attack from a hostile person or persons, with potential legal, social, and political implications. In a sense, the medical issues of a particular patient may take a back seat to the larger social and political issues at hand.\textsuperscript{98}
## Appendix A
### Characteristics of Selected Category A Agents

<table>
<thead>
<tr>
<th>Disease</th>
<th>Transmit person-to-person</th>
<th>Infective Dose (Aerosol)</th>
<th>Incubation time (days)</th>
<th>Duration of Illness</th>
<th>Fatality</th>
<th>Durability/Persistence of Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation anthrax</td>
<td>No</td>
<td>8,000-50,000 spores</td>
<td>1-6 d</td>
<td>3-5 days (fatal if untreated)</td>
<td>High</td>
<td>Very stable - spores remain viable for &gt; 40 years in soil</td>
</tr>
<tr>
<td>Pneumonic Plague</td>
<td>Yes</td>
<td>100-500 organisms</td>
<td>2-3 d</td>
<td>1-6 days (usually fatal)</td>
<td>High unless treated within 12-24 hours</td>
<td>For up to 1 year in soil; 270 days in live tissue</td>
</tr>
<tr>
<td>Tularemia</td>
<td>No</td>
<td>10-50 organisms</td>
<td>2-10 d (average 3-5)</td>
<td>≥ 2 weeks</td>
<td>Moderate if untreated</td>
<td>For months in moist soil or other media</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Yes</td>
<td>Assumed low (10-100 organisms)</td>
<td>7-17 d (average 12)</td>
<td>4 weeks</td>
<td>High to moderate</td>
<td>Very stable</td>
</tr>
<tr>
<td>VHF</td>
<td>Yes, weakly</td>
<td>1-10 organisms</td>
<td>4-21 d</td>
<td>Death between 7-16 days</td>
<td>High for Zaire strain, moderate with Sudan</td>
<td>Relatively unstable - depends on agent</td>
</tr>
<tr>
<td>Botulism</td>
<td>No</td>
<td>0.001 μg/kg is LD&lt;sub&gt;50&lt;/sub&gt; for type A</td>
<td>1-5 d</td>
<td>Death in 24-72 hours; lasts months if not lethal</td>
<td>High without respiratory support</td>
<td>For weeks in nonmoving water and food</td>
</tr>
</tbody>
</table>

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### Appendix B

**Quick Guide to selected BW Agents - Vaccine, Therapeutics, and Prophylaxis**

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>VACCINE</th>
<th>CHEMOTHERAPY (Rx)</th>
<th>CHEMOPROPHYLAXIS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td>Bioprt vaccine (licensed) 0.5 mL SC @ 0, 2, 4 wk, 6, 12, 18 mo then annual boosters</td>
<td>Ciprofloxacin 400 mg IV q 12 h or Doxycycline 200 mg IV, then 100 mg IV q 12 h</td>
<td>Ciprofloxacin 500 mg PO bid x 4 wk If unvaccinated, begin initial doses of vaccine</td>
<td>Potential alternates for Rx: gentamicin, erythromycin, and chloramphenicol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Penicillin 4 million units IV q 4 h</td>
<td>Doxycycline 100 mg PO bid x 4 wk plus vaccination</td>
<td>PCN for sensitive organisms only</td>
</tr>
<tr>
<td>Plague</td>
<td>Greer inactivated vaccine (FDA licensed) is no longer available.</td>
<td>Streptomycin 30 mg/kg/d IM in 2 divided doses x 10 - 14 d; or Gentamicin 5mg/kg or IV once daily x 10 - 14 d; or Ciprofloxacin 400mg IV q 12 h until clinically improved then 750 mg PO bid for total of 10 - 14 d</td>
<td>Doxycycline 100 mg PO bid x 7 d or duration of exposure</td>
<td>Chloramphenicol for plague meningitis is required 25 mg/kg IV, then 15 mg/kg qid x 14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doxycycline 200 mg IV then 100 mg IV bid, until clinically improved then 100mg PO bid for total of 10-14 d</td>
<td>Ciprofloxacin 500 mg PO bid x 7 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tetracycline 500 mg PO qid x 7 d</td>
<td>Alternate: trimethoprim-sulfamethoxazole</td>
<td></td>
</tr>
<tr>
<td>Tularemia</td>
<td>IND - Live attenuated vaccine: single 0.1ml dose by scarification</td>
<td>Streptomycin 7.5-10 mg/kg IM bid x 10-14 d</td>
<td>Doxycycline 100 mg PO bid x 14 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gentamicin 3-5 mg/kg/d IV x 10-14 d</td>
<td>Tetracycline 500 mg PO qid x 14 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ciprofloxacin 400 mg IV q 12h until improved, then 500 mg PO q 12 h for total of 10 - 14 d</td>
<td>Ciprofloxacin 500 mg PO q 12 h for 14 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ciprofloxacin 750 mg PO q 12 h for 10 - 14 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VHF s</td>
<td>AHF Candid #1 vaccine (x-protection for BHF) (IND)</td>
<td>Ribavirin (CCHF/Lassa) (IND) 30 mg/kg IV initial dose; then 16 mg/kg IV q 6 h x 4 d; then 8 mg/kg IV q 8 h x 6 d</td>
<td>NA</td>
<td>Aggressive supportive care and management of hypotension very important</td>
</tr>
<tr>
<td></td>
<td>RVF inactivated vaccine (IND)</td>
<td>Passive antibody for AHF, BHF, Lassa fever, and CCHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smallpox</td>
<td>Wyeth calf lymph vaccinia vaccine (licensed): 1 dose by scarification</td>
<td>No current Rx other than supportive; Ciclofivrin (effective in vitro); animal studies ongoing</td>
<td>Vaccinia immune globulin 0.6 mL/kg IM (within 3 d of exposure, best within 24 h)</td>
<td>Pre and post exposure vaccination recommended if &gt; 3 years since last vaccine</td>
</tr>
<tr>
<td>Botulism</td>
<td>DOD pentavalent toxoid for serotypes A - E (IND): 0.5 ml deep SC @ 0, 2 &amp; 12 wk, then yearly boosters</td>
<td>DOD heptavalent equine desecipated antitoxin for serotypes A-G (IND): 1 vial (10 mL) IV</td>
<td>NA</td>
<td>Skin test for hypersensitivity before equine antitoxin administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDC trivalent equine antitoxin for serotypes A, B, E (licensed)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix C—Dosing regimens

**Anthrax** \(^{30,50,51,54}\)
Anthrax is thought likely to be susceptible to the following antibiotics: rifampin, tetracycline, vancomycin, imipenem, meropenem, chloramphenicol, clindamycin, and the aminoglycosides. These may be selected while susceptibility testing pending and adjusted thereafter.

**Cutaneous anthrax**

Regimen

<table>
<thead>
<tr>
<th>Adults*</th>
<th>Ciprofloxacin 500 mg po bid or doxycycline 100 mg po bid x 60 days**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>Ciprofloxacin 10-15 mg/kg q12h (&lt;1 gm/d) or doxycycline in the following dose regimens: 8 yrs &amp; &gt;45 kg: 100 mg po q12h &gt;8 yrs &amp; &lt;45 kg or &lt;8 yrs: 2.2 mg/kg q12hr x 60 days** ***</td>
</tr>
</tbody>
</table>

**Inhalation anthrax**

Adult* Doxycycline 200 mg loading dose IV, then 100 mg IV q12h plus 1 or 2 other antibiotics**

Ciprofloxacin 400 mg IV q12h plus 1 or 2 other antibiotics**

Note: Switch to po therapy when clinically appropriate with Ciprofloxacin 500 mg bid or doxy 100 mg bid to complete 60 days therapy.

** Other antibiotics that are active in vitro against the current strain: ampicillin, penicillin, clindamycin, clarithromycin, imipenem, vancomycin, rifampin, chloramphenicol.

*** Consider steroids with severe edema or meningitis.

**** One drug may be used when patient has stabilized. Q-e

**Plague** \(^{10,67}\)

**Individual case**

Adults Streptomycin 30 mg/kg/day IM in two divided doses x 14 d; or Gentamicin, 5mg/kg IM or IV qd 14 d, or 2mg/kg loading dose followed by 1.75 mg/kg IM or IV q 8 hours; Doxycycline 200 mg initially, followed by 100 mg every 12 hours.

* The patient is typically afebrile after 3 days, but continued therapy prevents relapses.

* Animal studies indicate that quinolone antibiotics may also be effective.

Recommendations: Ciprofloxacin 400mg IV bid.

**Plague Meningitis**

Adults: Chloramphenicol 25 mg/kg IV loading dose, then 15 mg/kg IV qid x 10-14 days
**Plague Mass Infection or post exposure prophylaxis**
Adults: Doxycycline 100 mg orally bid.
*Ciprofloxacin 500 mg orally twice daily has also shown to effective in animal studies, and may be more available in a wartime setting as it is also distributed in blister packs for anthrax Post-exposure prophylaxis.

Alternatives:
Tetracycline, 500 mg po four times daily, and chloramphenicol, 25 mg/kg orally qid,

---

**Botulinum**

*Botulinum Antitoxin*
*a single 10-mL vial is used per patient,*
*it is diluted to 1:10 in 0.9% saline solution*
*it should be administered by slow intravenous infusion.*
*One vial provides between 5500 and 8500 IU of each type-specific antitoxin.*
*****The amount of neutralizing antibody far exceeds the highest serum toxin levels found in naturally occurring botulism patients, so no further administration is needed. In the context of deliberate attack with botulinum, it is possible that the serum concentrations could be far higher than in naturally occurring botulism. It may be necessary to retest the serum for toxin after initial treatment to assess if additional dosing would be of therapeutic value.

---

**Tularemia**

*Known infection*

*Individual case*
Adult: Streptomycin 1g IM bid, or
   Gentamycin 5mg/kg IM/IV bid.

Alternatives:
   Doxycycline 100 mg/kg IV bid
   Chloramphenicol 15mg/kg IV qid (not to be used in pregnant women)
   Ciprofloxacin 400mg IV bid

*Mass Infection or post exposure prophylaxis*
Adult Doxycycline 100 mg po bid
Ciprofloxacin 500 mg po bid
**VHF** 89,90

*Dosing of Ribavirin* *

**Indication:**
1. Patients with VHF with unknown pathogen
2. Pathogen known to be Arenavirus or Bunyavirus

**Individual case:**
Adult, pregnant women, children
Loading dose--30 mg/kg IV (max of 2 g) x 1, then
16 mg/kg IV (max of 1 g per dose) q 6 h x 4 d, then
8 mg/kg IV (max of 500 mg per dose) q 8 h x 6 days

*Mass Infection or post exposure prophylaxis*

Adult, pregnant women
Loading dose—2 g po x 1, then
If > 75 kg, 600 mg po bid x 10 days
If < 75 kg, 400 q am and 600 q pm x 10 days

* Not FDA approved
Appendix D: Specimens for Laboratory Diagnosis

The following is a selected list of samples to be collected, as is feasible, and sent for laboratory study in the case of a suspected infection with a biological agent.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Face or Nasal Swab(^1)</th>
<th>Blood Culture</th>
<th>Smear</th>
<th>Acute &amp; Convalescent Sera</th>
<th>Stool</th>
<th>Urine</th>
<th>Other</th>
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<tr>
<td>Anthrax</td>
<td>+</td>
<td>+</td>
<td>Pleural and CS fluids mediastinal lymph node spleen</td>
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<td>-</td>
<td></td>
<td>Cut. Lesion aspirates</td>
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<td>Plague</td>
<td>+</td>
<td>+</td>
<td>Sputum</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Bubo aspirate, CSF, sputum, lesion scraping, LN aspirate</td>
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<tr>
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<td>+(^1)</td>
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<tr>
<td>Clostridial Toxins</td>
<td>+</td>
<td>-</td>
<td>Wound tissues</td>
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<tr>
<td>Congo-Crimean Hemorrhagic Fever (VHF)</td>
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<td>+(^3)</td>
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<td>Liver</td>
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\(^1\)Virus isolation from blood or throat swabs in appropriate containment.

All samples should be sent to:

The Connecticut State Department of Health
Biological Science Services (860) 509-8505
10 Clinton Street
Hartford, CT 06106
(806) 509-8500

Collection Kits (860) 509-8501
For primary care physicians, the left hand column is the one of relevance. While the local public health authority should, ideally, make the initial assessment as to whether the particular case or cases are indeed a result of bioterrorism, the clinician must be skilled enough to do. If even one case is thought to be from a biowarfare source, the FBI must be notified. After federal law enforcement officials are notified (see criteria below), the State Health Department should be immediately notified. After the FBI and the state HD, then the CD should be contacted.

The CDC has set forth the following criteria for FBI notification:
A. one or more cases, definitively diagnosed with one or more of the following:
   1. Any case of smallpox or pulmonary anthrax.
   2. Uncommon agent or disease (e.g., smallpox, pulmonary anthrax) occurring in a person with no other explanation.
   3. An illness caused by a microorganism with markedly atypical features (e.g., features suggesting that the microorganism was genetically altered)
   4. An illness due to aerosol or food or water sabotage, as opposed to a usual transmission route.
B. one or more clusters of illnesses that are unexplained after preliminary investigation;
C. deliberate chemical, industrial, radiation or nuclear release.
Appendix F

Distinguishing naturally occurring forms from their use as biological weapons.

This is not a definitive or comprehensive list. Please note that these are meant to serve as possible signals to investigate further, not for drawing conclusions: there may be perfectly legitimate alternative explanations.

The following observations may raise the likelihood of a biological attack.

Clinical Findings
• The appearance of non-indigenous bacterial or viruses, or the appearance of unusual strains of indigenous microbes.
  Example-1. The identification of an Ebola strain in the United States, or Europe
  Ebola in euro, US
  Example-2. The identification of a tularemia strain showing broad antibiotic resistance.
• The sudden appearance of respiratory symptoms or cutaneous lesions in an otherwise healthy person from a healthy population
  Example-1. A 40 year old, otherwise healthy male, with pneumonic symptoms refractory to antibiotics for community acquired pneumonia.
• Multiple cases of the same symptom pattern or diagnosis.
  Example-1 More than 1 patient with a maculopular lesion and prodromal symptoms.
  Example-2. Multiple cases of ulceroglandular tularemia, which would suggest a contaminated food or water source
• Seasonal patterns may be factors; that is, it is useful to note whether cases are occurring in or out of seasonal cycles.
  Example-1. Cases of tularemia in early spring or fall rather than the natural seasonal occurrences of summer and winter.

Public health Findings
• An outbreak, even if zoonotic sources are possible, is less likely if distant outbreaks occur concurrently.
  Example. Bubonic plague outbreaks in New York City and in Seattle at the same time.
• The sudden appearance of an unusual form of a naturally occurring disease.
  Example. The identification of pneumonic forms of plague without any diagnosed cases of the bubonic form.
• A disproportionately high concentration of naturally occurring agents noted in samples of the environment.
  Example. Soil samples taken of botulinum show levels orders of magnitude higher than normal.
Possible indications of weaponized or modified agent

• An epidemic that spreads dramatically faster than is likely in naturally occurring outbreak. Please note that the rate of spread is a function of many factors including microbe virulence and concentration and also must be viewed in the context of what stage the epidemic is.
  Example. Rapidly spreading tularemia would be highly unusual
• If the disease course of a given microbe present is noted to be uncharacteristically rapid and/or severe.
• If resistance to appropriate and recommended antibiotic regimens is noted.
• If person-to-person transmission is noted with an illness that does not naturally do so.
  Example. The confirmation that botulism is spreading through close contacts
• Noting clustering of cases in a targeted population may be suggestive e.g. religious, ethnic, or other unifying features of a group
  Example. An outbreak of anthrax in a community, but no members of a white supremacist group or their families become infected.
Appendix G
Public Health Contact Information

Federal
CDC
24-hour Emergency Response Hotline (770) 448-7100.

Bioterrorism Preparedness and Response Program
(404) 639-0385

Clinician Information Line for Smallpox and Smallpox Vaccination
(877) 554-4625

CDC Clinician Registry for Terrorism and Emergency Response Updates and Training Opportunities:
http://www.bt.cdc.gov/clinregistry/index.asp

Email: cdcresponse@ashastd.org

FBI
Regional office
New Haven, Connecticut 06511-6505
(203) 777-6311

FBI Headquarters in Washington, D.C.
202-324-3000

State
Connecticut Department of Public Health
(860) 509-8000 – Emergency--Available 24 hours a day, 7 days a week

Bioterrorism Coordinator, Epidemiologist
James Hadler, MD Director Tel. (860) 509-7994/7995
Fax (860) 509-710

Bioterrorism Preparedness Coordinator
Warren Wollschlager Tel. (860) 509 7011
Fax (860) 509-710

Public Health Laboratory
Dr. Katherine Kelley, Director (860) 509-8500
kati.kelley@po.state.ct.us

Biological Science Services (860) 509-8505
Appendix H

Phone and Fax numbers for municipal public health departments:
State of Connecticut
<table>
<thead>
<tr>
<th>Town</th>
<th>Name</th>
<th>Phone</th>
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<tr>
<td>Andover</td>
<td>Rozann F. Venti, MD</td>
<td>(860) 742-0188</td>
<td>Fax: (860) 228-3766</td>
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<tr>
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<tr>
<td>Bethany</td>
<td>Ronald A. Zlotoff, MD, LLC</td>
<td>(203) 393-2100</td>
<td>Fax: (203) 755-8129</td>
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<tr>
<td>*Bethel</td>
<td>Laura Vasile, MPH, RS</td>
<td>(203) 794-8539</td>
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<tr>
<td>Bozrah</td>
<td>Michael G. Betten, MD</td>
<td>(860) 889-1239</td>
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<tr>
<td>Town of Bozrah</td>
<td>Town Hall: (860) 889-2689</td>
<td>Fax: (860) 889-1239</td>
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<td>*Bridgeport</td>
<td>Thomas E. Gecewicz, MPA, CHWM</td>
<td>(203) 576-7680</td>
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<tr>
<td>Director of Health</td>
<td>Town Hall: (203) 576-7201</td>
<td>Fax: (203) 576-8311</td>
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<tr>
<td>Bridgewater</td>
<td>Josef Burton, MD</td>
<td>(860) 355-4467</td>
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<tr>
<td>Director of Health</td>
<td>Town Hall: (860) 354-5102</td>
<td>Fax: (860) 350-4271</td>
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<td>*Bristol</td>
<td>Patricia J. Checko, MPH, DrPH</td>
<td>(860) 584-7682</td>
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<td>Director of Health</td>
<td>- Health Dept: (860) 584-3814</td>
<td>Town Hall: (860) 584-3814</td>
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<td>Brookfield</td>
<td>Claire Fee, MD</td>
<td>(203) 775-7315</td>
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<td>Director of Health</td>
<td>- Town Hall: (203) 775-7315</td>
<td>Fax: (203) 740-7677</td>
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<td>Central Connecticut Health District</td>
<td>Paul Hutchenson, MPH, RS</td>
<td>(860) 721-2822</td>
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<td>Director of Health</td>
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<tr>
<td>Chaplin</td>
<td>Peter Jones, MD</td>
<td>(860) 455-9455</td>
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<td>Town Hall: (860) 456-8288</td>
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<td>Chatham Health District</td>
<td>Thad D. King, MPH, RS</td>
<td>(860) 267-9601</td>
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<td>Chester</td>
<td>Russell Munson, MD</td>
<td>(860) 526-0009</td>
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<tr>
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<td>Director of Health: (203) 797-4500</td>
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<td>Robert L. Miller, MPH, RS</td>
<td>Health Dept: (860) 429-3325</td>
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<td>Richard H. Matheny, Jr., MPH, MFS, RS</td>
<td>Health Dept: (860) 676-1953</td>
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<tr>
<td></td>
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<td>Harold (Hal) Burdo, MPH</td>
<td>Town Hall: (860) 642-7352</td>
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*Glastonbury
David Boone, MPH RS  Health Dept: (860) 652-7534
Director of Health  Town Hall: (860) 652-7500
Email: boone@glasct.org  Fax: (860) 652-7734

*Goshen
See Torrington Area Health District

*Granby
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Hampton
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*Hartland
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*Harwinton
See Torrington Health District

*Hebron
See Chatham Health District

*Kent
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*Killingworth
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*Mansfield
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*Marlborough
See Chatham Health District

Mashantucket Pequot Health Department
Amarilis Rodriguez, MD  Health Dept: (860) 312-8032
Email: arodriguez@mptn.org  Fax: (860) 889-7557
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<td><strong>Beth Vumbaco, RN, MS</strong></td>
<td><strong>Health Dept:</strong> (203) 630-4221</td>
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<td><strong>Email:</strong> <a href="mailto:hvumbaco@ci.meriden.ct.us">hvumbaco@ci.meriden.ct.us</a></td>
<td><strong>Fax:</strong> (203) 639-0039</td>
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<td><strong>William P. Arnold, Jr., MD</strong></td>
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<td><strong>Director of Health</strong></td>
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<td><strong>Email:</strong> <a href="mailto:hoboinspec@ao.com">hoboinspec@ao.com</a></td>
<td><strong>Fax:</strong> (203) 598-7640</td>
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<td><strong>Adam Perrin, MD</strong></td>
<td><strong>Health Dept:</strong> (860) 349-7123</td>
<td><strong>Director of Health</strong></td>
<td><strong>Town Hall:</strong> (860) 349-7114</td>
<td><strong>Email:</strong> <a href="mailto:townsmiddlet04@snet.net">townsmiddlet04@snet.net</a></td>
<td><strong>Fax:</strong> (860) 349-8537</td>
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<tr>
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<td><strong>Fax:</strong> (860) 344-3588</td>
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<td><strong>Andrew Dennis McBride, MD, MPH</strong></td>
<td><strong>Health Dept:</strong> (203) 783-3285</td>
<td><strong>Director of Health</strong></td>
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<td><strong>Email:</strong> <a href="mailto:ADMcBride@ci.milford.ct.us">ADMcBride@ci.milford.ct.us</a></td>
<td><strong>Fax:</strong> (203) 783-3286</td>
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<tr>
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<td><strong>Fax:</strong> (860) 862-6189</td>
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<tr>
<td><strong>Judith Major, MD</strong></td>
<td><strong>Town Hall:</strong> (203) 452-5422</td>
<td><strong>Email:</strong> <a href="mailto:tmunks@monroect.org">tmunks@monroect.org</a></td>
<td><strong>Fax:</strong> (203) 452-2201</td>
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| *Montville     |                      |                 |                   |                      |                      |

| See Uncas Health District |                      |                 |                   |                      |                      |

| *Morris        |                      |                 |                   |                      |                      |

| See Torrington Area Health District |                      |                 |                   |                      |                      |

| *Naugatuck     |                      |                 |                   |                      |                      |

| See Naugatuck Valley Health District |                      |                 |                   |                      |                      |

| Naugatuck Valley Health District | **Health Dept:** (203) 924-9548 | **Director of Health** | **Town Hall:** (203) 924-8308 | **Email:** spargonvhd@aol.com | **Fax:** (203) 924-8308 |

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<tr>
<td><strong>Eugene Ciccone, MD</strong></td>
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<td><strong>Fax:</strong> (860) 826-3475</td>
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<td><strong>Harrison Joseph Pierce, MD</strong></td>
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<td><strong>Fax:</strong> (203) 594-3125</td>
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<td><strong>Timothy Simpkins, RS, MA</strong></td>
<td><strong>Health Dept:</strong> (203) 312-5640</td>
<td><strong>Director of Health</strong></td>
<td><strong>Town Hall:</strong> (203) 312-5600</td>
<td><strong>Email:</strong> <a href="mailto:dohnewfairfield@cthan.org">dohnewfairfield@cthan.org</a></td>
<td><strong>Fax:</strong> (203) 312-5608</td>
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<tr>
<td><strong>William P. Quinn, MPH</strong></td>
<td><strong>Health Dept:</strong> (203) 946-6999</td>
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<td><strong>Fax:</strong> (203) 946-7234</td>
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<td><strong>Pamela Kilby-Fox, MPH</strong></td>
<td><strong>Health Dept:</strong> (860) 447-5233</td>
<td><strong>Director of Health &amp; Social Services</strong></td>
<td><strong>Town Hall:</strong> (860) 447-5201</td>
<td><strong>Email:</strong> <a href="mailto:pkilby-fox@ci.new-london.ct.us">pkilby-fox@ci.new-london.ct.us</a></td>
<td><strong>Fax:</strong> (860) 447-5246</td>
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<td><strong>Michael A. Crespan, MPH, RS</strong></td>
<td><strong>Health Dept:</strong> (860) 355-6035</td>
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<td><strong>Fax:</strong> (860) 210-2664</td>
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<tr>
<td><strong>Shahnaz Hussain, MD</strong></td>
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<td><strong>Email:</strong> <a href="mailto:rcogrove@ci.newington.ct.us">rcogrove@ci.newington.ct.us</a></td>
<td><strong>Fax:</strong> (860) 665-8533</td>
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| *Newtown        |                      |                 |                   |                      |                      |
| See Newtown Health District |                      |                 |                   |                      |                      |

| Newtown Health District |                      |                 |                   |                      |                      |

| *Norfolk        |                      |                 |                   |                      |                      |

| See Torrington Area Health District |                      |                 |                   |                      |                      |

| *North Branford |                      |                 |                   |                      |                      |

| See East Shore Health District |                      |                 |                   |                      |                      |

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<tr>
<td><strong>Bruce D. Janelli, MD</strong></td>
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<td><strong>Email:</strong> <a href="mailto:nc.sanitarian@snet.net">nc.sanitarian@snet.net</a></td>
<td><strong>Fax:</strong> (860) 824-3139</td>
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North Central Health District

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<th>Name</th>
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<tr>
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<td>(860) 745-3188</td>
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*North Haven

See Quinnipiac Valley Health District

North Stonington

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<th>Name</th>
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<tr>
<td>Barbara Ann Deindorfer, MD</td>
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<td>(860) 535-4554</td>
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Northeast District Department of Health

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<th>Name</th>
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<tr>
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<td>(860) 774-1308</td>
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*Norwalk

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<tr>
<td>Timothy Callahan, MPH, RS</td>
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<tr>
<td>Director of Health</td>
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<tr>
<td>Email: <a href="mailto:tcallahan@norwalkct.org">tcallahan@norwalkct.org</a></td>
<td>Fax:</td>
<td>(203) 854-7934</td>
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*Norwich

See Uncas Health District

Old Lyme

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<tr>
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<tr>
<td>Email: <a href="mailto:vsikand@aol.com">vsikand@aol.com</a></td>
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Old Saybrook

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<tr>
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<tr>
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*Oxford

See Pomperaug Health District

*Plainfield

See Northeast District Department of Health

Plainville

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<td>Director of Health</td>
<td>Town Hall</td>
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*Plymouth

See Torrington Area Health District

*Pomfret

See Northeast District Department of Health

Pomperaug Health District

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<td>(203) 262-1960</td>
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Portland

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<th>Name</th>
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<tr>
<td>Linda G. Worden, RN, MPH</td>
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<tr>
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<td>Email: <a href="mailto:dmitchell@portlandct.org">dmitchell@portlandct.org</a></td>
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<td>Albert Gosselin, MD</td>
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<td><a href="mailto:algosselin@mindspring.com">algosselin@mindspring.com</a></td>
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<tr>
<td>*Prospect</td>
<td>Fax:</td>
<td>(860) 376-7070</td>
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See Chesproct Health District

Putnam

See Northeast District Department of Health

Quinnipiac Valley Health District

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<td>Leslie Balch, MPH</td>
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<tr>
<td>Email: <a href="mailto:lbalach@qvhdd.org">lbalach@qvhdd.org</a></td>
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<td>Matthew A. Miller, MD, FACP</td>
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<td>Director of Health</td>
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Ridgefield

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<td>Patrick Neligan, MD</td>
<td>Health Dept.</td>
<td>(203) 431-2745</td>
<td><a href="mailto:eh.health@ridgefieldct.org">eh.health@ridgefieldct.org</a></td>
</tr>
<tr>
<td>Director of Health</td>
<td>Town Hall</td>
<td>(203) 431-2745</td>
<td></td>
</tr>
<tr>
<td>Email: el健康的@ridgefieldct.org</td>
<td>Fax:</td>
<td>(203) 431-2737</td>
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*Rocky Hill

See Central Connecticut Health District

Roxbury

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Eric Salk, MD, MPH</td>
<td>Health Dept.</td>
<td>(860) 355-2985</td>
<td><a href="mailto:dishonest@ctan.org">dishonest@ctan.org</a></td>
</tr>
<tr>
<td>Director of Health</td>
<td>Town Hall</td>
<td>(860) 354-9938</td>
<td></td>
</tr>
<tr>
<td>Email: <a href="mailto:dishonest@ctan.org">dishonest@ctan.org</a></td>
<td>Fax:</td>
<td>(860) 354-0560</td>
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Salem

<table>
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<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Harold (Hal) Burdo, MPH</td>
<td>Town Hall</td>
<td>(860) 859-3873</td>
<td><a href="mailto:occumite@juno.com">occumite@juno.com</a></td>
</tr>
<tr>
<td>Email: <a href="mailto:occumite@juno.com">occumite@juno.com</a></td>
<td>Fax:</td>
<td>(860) 822-8002</td>
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*Salisbury

See Torrington Area Health District

Scotland

<table>
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<tr>
<th>Name</th>
<th>Position</th>
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<tbody>
<tr>
<td>Peter Jones, MD, FACP, PC</td>
<td>Town Hall</td>
<td>(860) 423-9634</td>
<td><a href="mailto:pjones@wcmh.org">pjones@wcmh.org</a></td>
</tr>
<tr>
<td>Email: <a href="mailto:pjones@wcmh.org">pjones@wcmh.org</a></td>
<td>Fax:</td>
<td>(860) 423-3666</td>
<td></td>
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*Seymour

See Naugatuck Valley Health District
<table>
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<tr>
<th>Location</th>
<th>Name</th>
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<th>Health Dept.</th>
<th>Town Hall</th>
<th>Fax</th>
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<tbody>
<tr>
<td><em>Shelton</em></td>
<td>See Naugatuck Valley Health District</td>
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</tr>
<tr>
<td><em>Sherman</em></td>
<td>Timothy Simpkins, MA, RS</td>
<td>Acting Director of Health</td>
<td>(860) 355-0166</td>
<td>(860) 355-0166</td>
<td>(860) 355-5041</td>
</tr>
<tr>
<td><em>Simsbury</em></td>
<td>See Farmington Valley Health District</td>
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<tr>
<td><em>Somers</em></td>
<td>Richard A. Segool, MD</td>
<td>Director of Health</td>
<td>(860) 763-8216</td>
<td>(860) 763-8206</td>
<td>(860) 763-8223</td>
</tr>
<tr>
<td><em>South Windsor</em></td>
<td>Gerald L. Schwartz, MD</td>
<td></td>
<td>(860) 644-2511</td>
<td>(860) 644-3781</td>
<td></td>
</tr>
<tr>
<td><em>Southbury</em></td>
<td>See Pomperaug Health District</td>
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<tr>
<td><em>Southington</em></td>
<td>Charles I. Motes, Jr., MS, MPH, RS</td>
<td>Director of Health</td>
<td>(860) 276-6275</td>
<td>(860) 276-6200</td>
<td>(860) 276-6277</td>
</tr>
<tr>
<td>Sprague</td>
<td>Harold (Hal) Burdo, MPH, RS</td>
<td>Director of Health</td>
<td>(860) 822-3010</td>
<td>(860) 822-3001</td>
<td>(860) 822-8002</td>
</tr>
<tr>
<td><em>Stafford</em></td>
<td>See North Central Health District</td>
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<tr>
<td><em>Stamford</em></td>
<td>Anthony Iton, MD, JD, MPH</td>
<td>Director of Health</td>
<td>(203) 977-4396</td>
<td>(203) 977-4150</td>
<td>(203) 977-5882</td>
</tr>
<tr>
<td><em>Sterling</em></td>
<td>See Northeast District Department of Health</td>
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<td></td>
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</tr>
<tr>
<td><em>Stonington</em></td>
<td>Michael Blefeld, MD</td>
<td></td>
<td>860-535-5075</td>
<td></td>
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Appendix H-1

Sample of PD-23 Form

To be used for reporting suspected case of Category A biological agents. To be filled out and sent within 12 hours as a confidential mailing. Please note: reporting by phone is required the same day to local and state public health departments. If deliberate exposure is suspected, the FBI must be notified.
The director of any clinical laboratory must report any laboratory evidence suggestive of reportable diseases. A standard form, known as the Laboratory Report of Significant Findings (OL-15C) is available for reporting these laboratory findings. These forms are available from the Connecticut Department of Public Health, Epidemiology Program, 410 Capitol Ave., MS#11EPI, P.O. Box 340308, Hartford, CT 06134-0308; telephone: (860-509-7994). The laboratory reports are not substitutes for physician reports; they are supplements to physician reports which allow verification of diagnosis. A special listing of diseases indicative of possible bioterrorism is highlighted at the end of this list. Changes for 2003 are noted in bold and with an asterisk (*).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test(s)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>CD4+ T-lymphocyte counts &lt;200 cells/L</td>
<td>Cell count</td>
</tr>
<tr>
<td>Babesiosis</td>
<td>IFA, IgM (titers)</td>
<td>Immunofluorescence assay</td>
</tr>
<tr>
<td>Blood smear</td>
<td>PCR, Other</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>Campylobacteriosis (species)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboxyhemoglobin ≥ 9%</td>
<td>%</td>
<td>Percentage</td>
</tr>
<tr>
<td>Chancroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chickenpox, acute</td>
<td>IgM, Culture, PCR</td>
<td>Immunoglobulin, Bacterial culture, Polymerase chain reaction</td>
</tr>
<tr>
<td>California group virus (species)</td>
<td>Eastern equine encephalitis virus</td>
<td></td>
</tr>
<tr>
<td>St. Louis encephalitis virus</td>
<td>West Nile virus infection – human or animal</td>
<td></td>
</tr>
<tr>
<td>Other arbovirus (specify)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcal infection, vancomycin-resistant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli O157 infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food poisoning (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giardiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonorrhea (test type):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A streptococcal disease, invasive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B streptococcal disease, invasive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae disease, invasive, all serotypes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hansen’s disease (Leprosy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>IgM anti-HAV</td>
<td>Immunoglobulin</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>HBsAg, IgM anti-HBc</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>(anti-HCV)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis delta</td>
<td>HDAg, IgM anti-HD</td>
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</tr>
<tr>
<td>HIV infection (report only to the State)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 infection in person ≥ 13 years of age (5)</td>
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<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>A, B</td>
<td></td>
</tr>
<tr>
<td>Lead poisoning (blood lead ≥ 10 μg/dL)</td>
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<td></td>
</tr>
<tr>
<td>Legionellosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Listeriosis (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria/blood parasites (1,2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles (Rubella) (titer):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal disease, invasive (1,3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury poisoning</td>
<td></td>
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</tr>
<tr>
<td>Pertussis (titer):</td>
<td></td>
<td>Immunoglobulin</td>
</tr>
<tr>
<td>Pneumococcal disease, invasive (1,3)</td>
<td>Oxacillin disk zone size:</td>
<td>Diameter</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabies</td>
<td></td>
<td></td>
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<tr>
<td>Rocky Mountain spotted fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubella (titer):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonellosis (1,2) (serogroup/serotype)</td>
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<td></td>
</tr>
<tr>
<td>Staphylococcus epidermidis infection with MIC to vancomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus infection with MIC to vancomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus disease, invasive (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>RPR (titer):</td>
<td>Immunoglobulin</td>
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<tr>
<td>Trichinosis</td>
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<tr>
<td>Tuberculosis (1)</td>
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<tr>
<td>Typhus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vibrio infection (6) (species)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yersiniosis</td>
<td></td>
<td></td>
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</table>

Diseases that are possible indicators of bioterrorism.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
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<tbody>
<tr>
<td>Anthrax</td>
<td></td>
</tr>
<tr>
<td>Botulism</td>
<td></td>
</tr>
<tr>
<td>Brucellosis</td>
<td></td>
</tr>
<tr>
<td>Gram positive rod septicemia or meningitis, growth within 72 hours of inoculation*</td>
<td></td>
</tr>
<tr>
<td>Plague</td>
<td></td>
</tr>
<tr>
<td>Ricin poisoning</td>
<td></td>
</tr>
<tr>
<td>Staphylococcal enterotoxin B pulmonary poisoning</td>
<td></td>
</tr>
<tr>
<td>Typhus</td>
<td></td>
</tr>
<tr>
<td>Viral hemorrhagic fever</td>
<td></td>
</tr>
</tbody>
</table>

1. Send isolate culture or slide to the State Laboratory for confirmation. For Shiga-toxin, send broth culture from which positive Shiga-toxin test was made.
2. Specify etiologic agent.
3. Invasive disease: confirmed by isolation from blood, CSF, pericardial fluid, pleural fluid, peritoneal fluid, joint fluid, bone, bone normally sterile sites, and intraoperative swabs from a normally sterile site or normally sterile tissue obtained during surgery.
4. Report all tests indicative of HIV infection including antibody, antigen, PCR based and viral load tests with name and street address.
5. Report only confirmed HIV antibody tests or positive HIV antigen tests with name and street address. Viral load and PCR-based test results not reportable for this age group.
6. Send V. cholerae, V. parahaemolyticus, and V. vulnificus isolates to the State Laboratory for confirmation.
7. Report only IgG titers that are considered significant by the laboratory performing the test.
Appendix I (patient handout)
Resources for Patients on bioterrorism

American Psychiatric Association
Coping with Bioterrorism Anxiety
http://www.psych.org/disaster/copingnationaltragedy-main92501.cfm
This is a useful site for patient’s to read about constructive ways of dealing with anxiety regarding bioterrorism.

American Red Cross
American Red Cross Homeland Security Advisory System Recommendations for Individuals, Families, Neighborhoods, Schools and Businesses.

Department of Homeland Security
http://www.ready.gov/biological.html
http://www.ready.gov/biological_threat.html
http://www.ready.gov/biological_symptoms.html
Ready. Gov is a web site run by the DHS that provides basic instructions and printable visual aids for strategies to be safe during an attack, and how to recognize signs of infection. Instructions are available for assembling “emergency kits”

Connecticut Department of Public Health
http://www.dph.state.ct.us/
Has useful links for bioterrorism locally and nationally.

Federal Emergency Management Agency
Are You Ready? A Guide to Citizen Preparedness. Provides information on bioterrorism as well as other man-made disasters and natural disaster, too. This is the source of the oft cited, recommendations for duct tape and plastic sheets.

Substance Abuse and Mental Health Services Administration
The Center for Mental Health Services' Disaster Mental Health homepage

American College of Physicians
Bioterrorism and Antibiotics - What You Should Know
http://www.acponline.org/bioterro/antibiotics.htm
Discusses the role of antibiotics in the event of a bioterrorist attack.
How to Tell Cold or Flu Symptoms from Inhalational Anthrax
http://www.acponline.org/bioterro/info_patients.htm
Explains ways to distinguish common types of respiratory infections from inhalational anthrax.
Frequently Asked Questions About Smallpox (handout?)
http://www.acponline.org/bioterro/faq_smallpox.htm
Answers basic but important questions about smallpox infection and vaccination.
Center for Disease Control
http://www.bt.cdc.gov/
The CDC is the definitive source for bioterrorism information. Offers information for patients and clinicians on every all topics relating to bioterrorism. Easy to use.
Appendix J

Online Resources for Physicians

Center for Disease Control and prevention CDC
http://www.bt.cdc.gov/
A portal to all the latest information on any and all bioterrorism related topics, as well as trainings and educational materials. CME credits are attainable.
They also offer an email registry that sends information on biological agents, updates on information, as well as announcements of available trainings-onsite and offsite. To register: http://www.bt.cdc.gov/clinregistry/index.asp

CDC Clinician Information Line for Smallpox and Smallpox Vaccination
(877) 554-4625

CDC Clinician Registry for Terrorism and Emergency Response Updates and Training Opportunities:
http://www.bt.cdc.gov/clinregistry/index.asp

Email: cdcresponse@ashastd.org

American College of Physicians online
http://www.acponline.org/bioterror/?hp
A great site for getting the fundamentals for diagnosis and management of the major Category A agents as well chemical agents. Also provides links to other resources

Connecticut State Department of Health
http://209.150.7.232/infoHealthCareProviders.shtml
Offers a variety of links on response strategies at the state and local levels as well as links to federal planning. A directory of state and local public health officials is available.

Center for Civilian Biodefense Studies, John Hopkins University
http://www.hopkins-biodefense.org/index.html
Based at Johns Hopkins University, this is the online information provided by the premiere non-governmental group working on Bioterrorism. Provides information on biological agents, provides the latest strategy developments, recommended reading, and links.

Virtual Naval Hospital
http://www.vnh.org
The US Navy’s online medical resource: Virtual Naval Hospital. The information is concise, up to date and well organized and covers a wider array of topics.

The US Army Medical Research Institute of Infectious Diseases (USAMRIID)
http://www.biomedtraining.org/proginfo.htm
Offers off-site civilian trainings on tape and through live broadcasts on various areas of bioterrorism. CME accreditation is available.

http://www.bioterrorism.uab.edu/
A site specifically for educating primary care physicians on bioterrorism provides images, self-tests, and links for more resources.
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