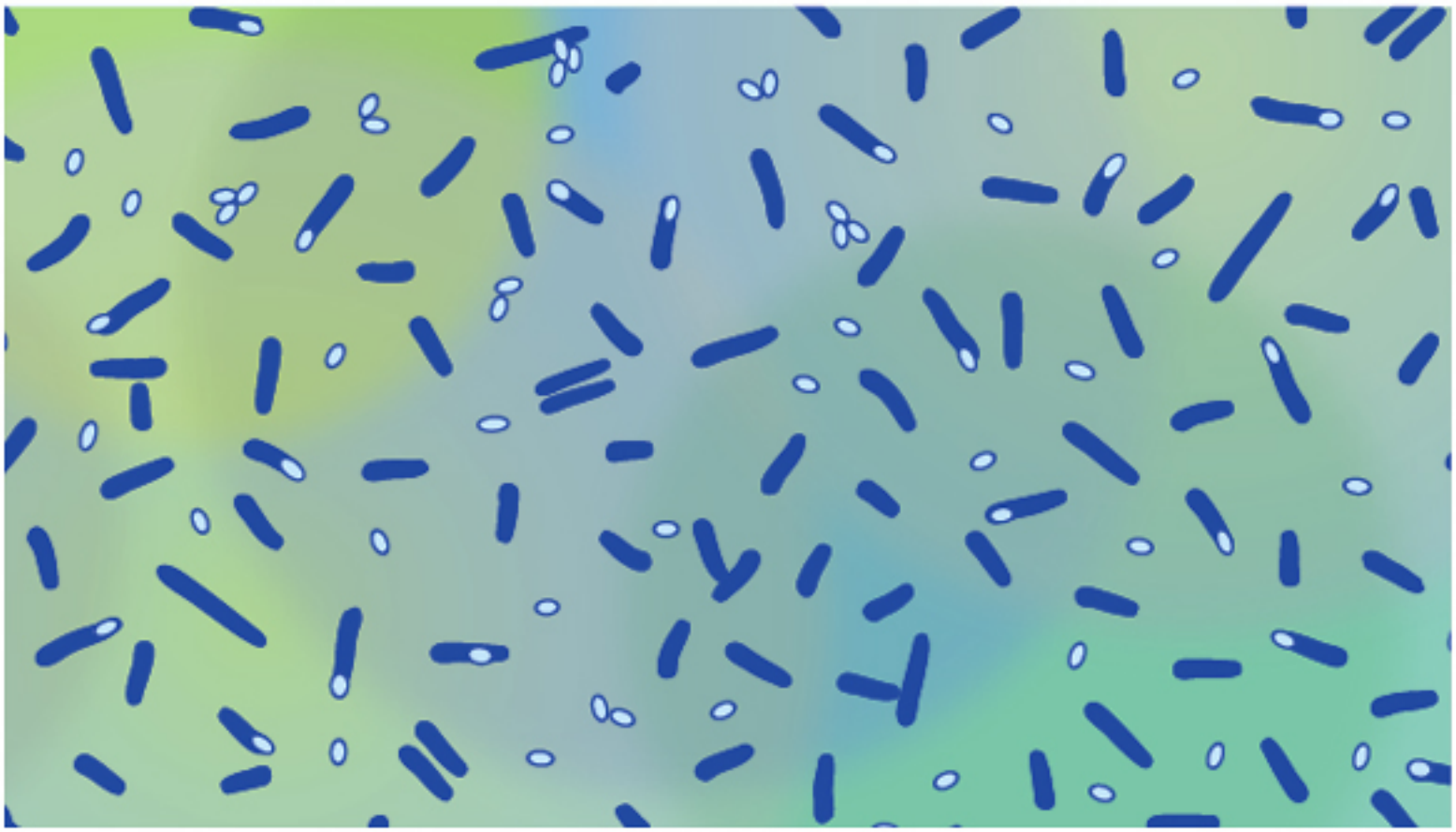
San Francisco Department Of Public Health

Infectious Disease Emergencies

A Preparedness And Response Guide
For San Francisco Clinicians



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City and County of San Francisco

San Francisco Department of Public Health

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Mayor

Communicable Disease Control & Prevention
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www.sfcdcp.org

July 30, 2008

Dear San Francisco Clinician,

Monitoring and controlling infectious disease outbreaks is a priority for the San Francisco Department of Public Health (SFDPH). Routine infectious disease emergencies vary in scope from a single case of meningococcal meningitis, to a case of hepatitis A in a food handler, to an outbreak of influenza in a nursing home. In San Francisco, prompt clinician reports of relevant clinical cases enable us to investigate and begin disease control activities as soon as possible.

To improve control of relatively common outbreaks and to improve recognition and response to emerging infectious diseases or diseases possibly related to bioterrorism, the Sentinel Event Enhanced Passive Surveillance (SEEPS) Project developed the enclosed reference: *Infectious Disease Emergencies: A Preparedness and Response Guide for San Francisco Clinicians*. This reference is provided in both hard copy binder format and electronically on our website (www.sfcdcp.org).

Throughout the US, clinicians have been the first to confront and alert public health officials to emerging infections, bioterrorism attacks, and widespread outbreaks. Please familiarize yourself with the contents of this guide to learn:

1. How SFDPH works to contain infectious diseases
2. Your role in reporting infectious diseases
3. Which diseases you should report to the health department
4. Your role in an infectious disease emergency
5. How to prepare for infectious disease emergencies
6. How to recognize and respond to potential bioterrorism agents and emerging infectious diseases

Currently, SFDPH alerts and updates clinicians on important public health infectious disease threats via fax using our Health Alert Notification Database (HAND) and by posting materials on our website.

- Sign up for inclusion in our HAND if you are not yet registered or if you would like to update your contact information. See instructions in the guide.
- Visit and bookmark our website (www.sfcdcp.org).

Working together, clinicians and SFDPH can better protect the health of all San Franciscans.

Thank you for your efforts.

Sincerely,

Mitch Katz, MD
Director
San Francisco Dept. of Public Health

Susan Fernyak, MD, MPH
Director
Communicable Disease Control & Prevention Section

HOW TO USE THIS GUIDE

This reference guide seeks to provide a comprehensive resource to assist clinicians in preparing for, recognizing, and responding to infectious disease emergencies. In the event of an infectious disease emergency, the San Francisco Department of Public Health will supplement the information in this guidebook with updates that will be faxed to clinicians and posted at: **www.sfcdcp.org/healthalerts.**

Use of this guide by San Francisco clinicians will strengthen surveillance for, and reporting of, certain critically important infectious diseases. Throughout the US, clinicians have been the first to confront and alert public health officials to emerging infections, bioterrorism attacks, and widespread outbreaks. In San Francisco the Department of Public Health relies daily on clinicians to recognize, respond to, and report infectious diseases. In an emerging infectious disease outbreak or bioterrorist attack these duties are especially critical.

This reference guide is divided into the following sections:

Tab 1	**Roles & Responsibilities** Roles and responsibilities of the Department of Public Health and San Francisco clinicians in an emergency
Tab 2	**What to Report** List of legally reportable diseases and contact information List of unusual conditions to report
Tab 3	**Preparing for Infectious Disease Emergencies** Guidance for preparing family, home, and office for an infectious disease emergency
Tab 4	**High Priority Diseases** Detailed information on potential bioterrorism related diseases and emerging infectious diseases
Tab 5	**Infection Control Guidelines** Description of standard, contact, droplet, and airborne precautions
Tab 6	**Appendix** Useful reporting forms and important regulations

An electronic copy of this guide is available at the SFDPH Communicable Disease Control & Prevention website:

www.sfcdcp.org/publications

The guide is modular and updates will be made as new information becomes available. To access the latest information visit the SFDPH Communicable Disease Control & Prevention website and review or download the most up-to-date materials.

CONTACT INFORMATION

Communicable Disease Control & Prevention

DISEASE REPORTING

Communicable Disease Reporting
(except TB, STDs, HIV/AIDS)

☎ (415) 554-2830 24/7
🖷 (415) 554-2848 fax
Communicable Disease Control Unit
101 Grove Street, Room 408
San Francisco, CA 94102
cdcontrol@sfdph.org

HIV/AIDS Reporting

☎ (415) 554-9050
🖷 (415) 431-0353 fax

STD reporting

☎ (415) 487-5555
🖷 (415) 431-4628 fax

TB Reporting

☎ (415) 206-8524
🖷 (415) 648-8369 fax

Foodborne Illness Reporting

Suspected food poisoning

☎ (415) 554-2830
🖷 (415) 554-3875 fax

Outbreaks of foodborne illness involving 4 or more persons

☎ (415) 554-2830
🖷 (415) 554-3875 fax

Animal Bite Reporting (mammals only)

☎ (415) 554-9422
☎ (415) 554-9400 24/7
🖷 (415) 864-2866 fax

COMMUNICABLE DISEASE CONTROL & PREVENTION OFFICES

Bioterrorism & Infectious Disease Emergencies Unit

☎ (415) 554-2818
🖷 (415)554-2854 fax
101 Grove Street, Room 204
San Francisco, CA 94102
www.sfcdcp.org/idemergencies

Communicable Disease Control Unit

☎ (415) 554-2830
🖷 (415) 554-2848 fax
101 Grove Street, Room 408
San Francisco, CA 94102
www.sfcdcp.org/diseasecontrol

Communicable Disease Prevention Unit

☎ (415) 554-2830
🖷 (415) 554-2848 fax
101 Grove Street, Room 408
San Francisco, CA 94102
www.sfcdcp.org/izs

CONTACT INFORMATION

Frequently Called Numbers

Animal Bite Reporting
Animal Care & Control
☎ (415) 554-9422
☎ (415) 554-9400 24-hour emergency dispatch

Bat Concerns
Animal Care & Control
☎ (415)554-9400 24-hour emergency dispatch

Dead Bird Testing for West Nile Virus
California Department of Health Services
☎ (877) WNV-BIRD (968-2473)

HIV Testing Services
Anonymous/confidential HIV counseling, testing, linkages, referrals, and appointments
☎ (800) 367-AIDS (2437)
9a-5p: M, W, Th, F; 9a-9p: T

Influenza Hotline
Communicable Disease Prevention Unit, SFDPH
☎ (415) 554-2681

Mosquito Control Problems
Environmental Health Services, SFDPH
☎ (415) 252-3806

Needlestick Hotline
National Coalition Consultation Center
☎ (888) 448-4911 (Consultation for clinicians, post-exposure prophylaxis hotline)

Restaurant Sanitation Complaints
Environmental Health Services, SFDPH
☎ (415) 252-3800

Rodents or Insect Infestations
Environmental Health Services, SFDPH
☎ (415) 252-3800

Sewage Leak
Environmental Health Services, SFDPH
☎ (415) 252-3800

Sexually Transmitted Diseases
STD Clinic, SFDPH
☎ (415) 487-5500

Suspected Food Poisoning Reporting
(less than 4 people ill)
Environmental Health Section, SFDPH
☎ (415) 252-3895

Travel Immunizations
Adult Immunization Clinic, SFDPH
☎ (415) 554-2625

Tuberculosis (TB)
TB Clinic, SFDPH
☎ (415) 206-8524

Unsanitary Living Conditions
Environmental Health Services, SFDPH
☎ (415) 252-3805

CONTACT INFORMATION

San Francisco Department of Public Health (SFDPH) Offices

SFDPH MAIN

San Francisco Department of Public Health

(415) 554-2500 main number
San Francisco Dept of Public Health
101 Grove Street, Room 100
San Francisco, CA 94102
www.sfdph.org

SFDPH OFFICES

AIDS Office

(415) 554-9000
25 Van Ness, 5th Floor
San Francisco, CA 94102

Communicable Disease Control & Prevention Section

(415) 554-2830
(415) 554-2848 fax
101 Grove Street, Room 408
San Francisco, CA 94102
www.sfcdcp.org

Emergency Medical Services Section

(415) 355-2600
(415) 552-0194 fax
68 12th Street, Suite 220
San Francisco, CA 94103
www.sanfranciscoems.org

Environmental Health Section

(415) 252-3800
1390 Market Street, Suite 210
San Francisco, CA 94102
www.sfdph.org/eh

SF Public Health Laboratory

(415) 554-2800
(415) 431-0651 fax
101 Grove Street, Room 419
San Francisco, CA 94102

STD Prevention & Control

(415) 487-5500
(415) 437-9231 fax
356 7th Street
San Francisco, CA 94103

Tuberculosis Control Section

(415) 206-8524
(415) 648-8369 fax
SFGH Bldg 90, 4th floor (Ward 94)
2460 22nd Street
San Francisco, CA 94110

WHAT HAPPENS WHEN YOU REPORT A DISEASE

The Communicable Disease Control Unit maintains a reporting telephone line to respond to clinician infectious disease reports 24 hours a day, 7 days a week. There are over 80 legally reportable diseases and conditions in San Francisco. Certain critical diseases must be reported within one hour to the Department of Public Health while others require same day notification or notification within one week. See the list of legally reportable diseases in the *What to Report* section.

After we receive an infectious disease report we immediately take action to protect the health of San Franciscans and our visitors.

COMMUNICABLE DISEASE REPORTING

Urgent Reports 24/7

☎ (415) 554-2830

After hours, follow prompts to page the on-call physician

Non-Urgent Reports

☎ (415) 554-2830
🖷 (415) 554-2848 fax
cdcontrol@sfdph.org
101 Grove Street, Room 408
San Francisco, CA 94102

Business hours: Mon - Fri 8 am - 5 pm

HOW WE RESPOND TO INFECTIOUS DISEASE REPORTS….

✓ INVESTIGATION

- **Case Investigation.** Interview cases and clinicians to identify risk factors and other potential contacts. Evaluate patients/contacts in sensitive occupations or settings that may pose a public health concern (e.g. food handlers, daycare attendees, health care workers or employees of group residential facilities).
- **Source Investigation.** Conduct an epidemiologic investigation to identify the source of infection and how it is being spread.
- **Lab Testing.** Provide guidance on obtaining lab tests to confirm diagnosis. Facilitate approvals for obtaining specialized tests performed at city, state, or federal public health labs.

✓ INFECTION CONTROL

- **Recommendations.** Work with infection control practitioners to recommend measures to control and prevent the spread of disease in healthcare settings.
- **Information & Education.** Provide information to cases, contacts, and the general public to prevent and control the spread of disease in community settings. In the event of an infectious disease emergency, provide continued infection control guidance and recommendations.
- **State & National Notification.** Coordinate notification of state and national health officials and law enforcement, as necessary.

✓ TREATMENT RECOMMENDATIONS

- **Postexposure & Preventive Treatment.** Assess the need for, and recommend preventive treatments such as antibiotics and vaccines. In case of mass exposure to a treatable infectious agent, activate the local system for providing mass treatment and/or prophylaxis.

✓ COMMUNICATION WITH CLINICIANS

- **Health Alerts.** Send Health Alerts, Advisories, and Updates to clinicians regarding infectious disease situations of public health concern.
- **Analysis of Surveillance Data.** Analyze and disseminate public health surveillance data to clinicians and the general public.

CLINICIAN ROLES IN AN EMERGENCY

Clinicians perform many roles during infectious disease emergencies. Many actions assist the San Francisco Department of Public Health (SFDPH) with timely investigations and effective public health interventions. Other actions mitigate the need for patient treatment at acute care sites, address concerns of the worried well, and maintain continuity of care for patients ill with diseases unrelated to the emergency.

KEY CLINICIAN ROLES

1. **Recognize** an infectious disease emergency.

- See *What to Report* and *Unusual Conditions to Report* to learn more about what we consider infectious disease emergencies.
- See the *High Priority Disease* chapters and the "BT Syndrome Poster" to learn how to recognize certain critical diseases.

2. **Respond** appropriately including implementation of infection control measures, initiation of diagnostic testing and therapy and prophylaxis (if needed).

- Familiarize yourself with initial patient management protocols and infection control measures. See the *Infection Control* and *High Priority Disease* chapters.
- Visit and bookmark the Communicable Disease Control and Prevention website: www.sfcdcp.org.
- Register to receive Health Alerts from SFDPH. See instructions in the appendix.

3. **Report** the incident to response partners.

- Keep SFDPH contact information and the names and contact information of your hospital infection control professionals handy.

SFDPH Communicable Disease Reporting

☎ (415) 554-2830 *24/7*
🖷 (415) 554-2848 fax

EMERGENCY TO DO LIST

Initial Steps

- ❑ Implement infection control measures
  - o If patient is in the hospital, notify Infection Control
- ❑ Notify SFDPH
- ❑ Notify your clinical lab and ensure appropriate specimens are obtained for routine and referral testing. Referral testing may be coordinated through the Public Health Lab system
- ❑ Initiate patient management
- ❑ If present, request that family and other contacts remain for public health interviews and prophylaxis if needed
- ❑ Ensure that family and contacts are educated about infection prevention
- ❑ If family or other close contacts are not present, obtain their contact information to provide to SFDPH

Subsequent Steps

- ❑ Follow incident progress and recommendations via SFDPH Health Alerts and/or our website: www.sfcdcp.org
- ❑ Make sure that your family, your staff, and the families of your staff are safe
- ❑ Keep office open unless advised otherwise
- ❑ Educate patients about measures to prevent exposure and disease
- ❑ Assess and care for the worried well

REPORTABLE DISEASES AND CONDITIONS

City and County of San Francisco San Francisco Department of Public Health

Title 17, California Code of Regulations (CCR) §2500, §2593, §2641-2643 and §2800-2812 §2500(b).
Every health care provider, knowing of or in attendance on a case or suspected case of any of the diseases or conditions listed below, must report to the local health officer for the jurisdiction where the patient resides. Where no health care provider is in attendance, any individual having knowledge of a person who is suspected to be suffering from one of the diseases or conditions listed below may make such a report to the local health officer for the jurisdiction where the patient resides.

WHO TO REPORT TO

REPORT OUTBREAKS, DISEASES, AND CONDITIONS TO* COMMUNICABLE DISEASE CONTROL UNIT *UNLESS OTHERWISE INDICATED

COMMUNICABLE DISEASE CONTROL UNIT
PHONE: (415) 554-2830 FAX: (415) 554-2848
M-F 8AM to 5PM
For urgent reports after hours, follow the prompts to page the on-call MD

AIDS OFFICE
PHONE: (415) 554-9050

STD CLINIC
PHONE: (415) 487-5555 FAX: (415) 431-4628

TUBERCULOSIS CLINIC
PHONE: (415) 206-8524 FAX: (415) 648-8369

ANIMAL BITES (mammals only)
PHONE: (415) 554-9422 FAX: (415) 864-2866

ENVIRONMENTAL HEALTH SERVICES
PHONE: (415) 252-3862 FAX: (415) 252-3818

DISEASE OR CONDITION / URGENCY REPORTING REQUIREMENTS

URGENCY REPORTING KEY
▲ Report immediately by telephone 1 Report within one working day of identification 7 Report within seven calendar days by FAX, phone or mail

- 7 Acquired Immune Deficiency Syndrome (AIDS) *to AIDS Office*
- 7 Alzheimer's Diseases and Related Conditions
- 1 Amebiasis
- 7 Animal bites (mammals only) *to Animal Care and Control*
- ▲ Anthrax*
- ▲ Avian Influenza (human)
- 1 Babesiosis
- ▲ Botulism* (Infant, Foodborne, Wound)
- ▲ Brucellosis*
- 1 Campylobacteriosis
- 7 Cancer, including benign and borderline brain tumors (except (1) basal and squamous skin cancer unless occurring on genitalia, and (2) carcinoma in-situ and CIN III of the cervix)
- 7 Chancroid *to STD Clinic*
- 1 Chickenpox (only hospitalizations and deaths)
- 7 Chlamydial infections *to STD Clinic*
- ▲ Cholera
- ▲ Ciguatera Fish Poisoning
- 7 Coccidioidomycosis
- 1 Colorado Tick Fever
- 1 Conjunctivitis, Acute Infectious of the Newborn (specify etiology)
- 7 Creutzfeldt-Jakob Disease (CJD)
- 1 Cryptosporidiosis
- 7 Cysticercosis
- ▲ Dengue
- ▲ Diarrhea of the Newborn, outbreaks
- ▲ Diphtheria
- 7 Disorders Characterized by Lapses of Consciousness
- ▲ Domoic Acid Poisoning (Amnesic Shellfish Poisoning)
- 7 Ehrlichiosis
- 1 Encephalitis, infectious (specify etiology)
- ▲ *Escherichia coli* shiga toxin producing (STEC) including *E. coli* O157
- ▲ Foodborne illness (2 or more cases from different households)
- 7 Giardiasis
- 7 Gonococcal infections *to STD Clinic*
- 1 *Haemophilus influenzae* invasive disease (less than 15 years of age)
- ▲ Hantavirus infections
- ▲ Hemolytic Uremic Syndrome
- 7 Hepatitis, viral
- 1 Hepatitis A
- 7 Hepatitis B (specify acute case or chronic)
- 7 Hepatitis C (specify acute case or chronic)
- 7 Hepatitis D (Delta)
- 7 Hepatitis, other acute
- 7 Human Immunodeficiency Virus (HIV) *to AIDS Office*
- 7 Influenza deaths (less than 18 years of age)
- 7 Kawasaki Syndrome (Mucocutaneous Lymph Node Syndrome)
- 7 Legionellosis
- 7 Leprosy (Hansen Disease)
- 7 Leptospirosis
- 1 Listeriosis
- 7 Lyme Disease
- 7 Lymphogranuloma Venereum (LGV) *to STD Clinic*
- 1 Malaria
- 1 Measles (Rubeola)
- 1 Meningitis (specify etiology)
- ▲ Meningococcal infections
- 7 Mumps
- ▲ Paralytic Shellfish Poisoning
- 7 Pelvic Inflammatory Disease (PID) *to STD Clinic*
- 1 Pertussis (Whooping Cough)
- 7 Pesticide-related illness or injury (known or suspected cases) to *Environmental Health Services*
- ▲ Plague (human or animal)*
- 1 Poliomyelitis, Paralytic
- 1 Psittacosis
- 1 Q Fever
- ▲ Rabies (human or animal)
- 1 Relapsing Fever
- 7 Rheumatic Fever, Acute
- 7 Rocky Mountain Spotted Fever
- 7 Rubella (German Measles)
- 7 Rubella Congenital Syndrome
- 1 Salmonellosis (other than Typhoid Fever)
- ▲ Scombroid Fish Poisoning
- ▲ Severe Acute Respiratory Syndrome (SARS)
- ▲ Shiga toxin (detected in feces)
- 1 Shigellosis
- ▲ Smallpox (Variola)*
- ▲ *Staphylococcus aureus* infections, severe (ICU/death) in a previously healthy person
- 1 Streptococcal infections, outbreaks of any type and individual cases in food handlers and dairy workers only
- 1 Syphilis *to STD Clinic*
- 7 Taeniasis
- 7 Tetanus
- 7 Toxic Shock Syndrome
- 7 Toxoplasmosis
- 7 Transmissable Spongiform Encephalopathies (TSE)
- 1 Trichinosis
- 1 Tuberculosis *to Tuberculosis Clinic*
- ▲ Tularemia*
- 1 Typhoid Fever (cases and carriers)
- 7 Typhus Fever
- 1 *Vibrio* infections
- ▲ Viral Hemorrhagic Fevers* (e.g. Crimean-Congo, Ebola, Lassa and Marburg viruses)
- 1 Water-associated disease (e.g. Swimmer's Itch and Hot Tub Rash)
- 1 West Nile Virus
- ▲ Yellow Fever
- 1 Yersiniosis
- ▲ **ANY UNUSUAL DISEASES**
- ▲ **NEW DISEASE OR SYNDROME NOT PREVIOUSLY RECOGNIZED**
- ▲ **OUTBREAKS OF ANY DISEASE**

*Potential Bioterrorism Agents

UNUSUAL CONDITIONS TO REPORT

The San Francisco Department of Public Health (SFDPH) depends on clinicians to identify and report cases of communicable diseases. Clinicians may be the first to see a potential outbreak in the making and their prompt notification to SFDPH enables us to investigate and begin disease control activities as soon as possible. For some diseases every hour makes a difference in preventing illness and death.

To improve our ability to control outbreaks the Sentinel Event Enhanced Passive Surveillance (SEEPS) Project works to strengthen clinicians' ability to identify emerging infectious diseases and those that may result from biological terrorism. Due to their deadliness it is particularly important that cases are recognized, diagnosed, and reported quickly. Knowing the clinical features and maintaining an index of suspicion for unusual cases and reporting them to SFDPH could save lives. Potentially unusual patterns of disease include:

COMMUNICABLE DISEASE REPORTING

Urgent Reports 24/7

☎ (415) 554-2830

After hours, follow prompts to page the on-call physician

Non-urgent Reports

☎ (415) 554-2830
🖷 (415) 554-2848 fax
cdcontrol@sfdph.org
101 Grove Street, Room 408
San Francisco, CA 94102

Business Hours: Mon - Fri 8 am - 5 pm

1. **Multiple similarly presenting cases, especially if these are geographically associated or closely clustered in time**
   Example: persons who attended the same event or who work in the same building

2. **An increase in a common syndrome occurring out of season**
   Example: many cases of influenza-like illness in summer

3. **An unusual age distribution for common diseases**
   Example: many cases of chickenpox-like illness in adult patients expected to be immune

4. **Serious, unexpected, unexplained acute illness with atypical host characteristics**
   Examples: severe illness in a young patient without immunologic defects, underlying illness, recent travel or other exposure to a potential source of infection†

Due to their rarity, some of the following diseases and conditions may not be immediately recognizable. However, maintaining a reasonable index of suspicion and reporting unusual conditions could assist in treating patients and safeguarding the public.

IMMEDIATE NOTIFICATION REQUIRED TO SFDPH (within one hour)

- Anthrax*
- Botulism*
- Brucellosis*
- Plague*
- Smallpox*
- Tularemia*
- Viral hemorrhagic fevers*
- Meningococcal infections
- Measles
- Avian Influenza
- SARS
- Diphtheria
- Hantavirus infections
- Yellow fever
- Shiga toxin producing *E. coli* (STEC) including *E. coli* 0157
- Shiga toxin (in feces)
- Hemolytic Uremic Syndrome
- Scombroid fish poisoning
- Ciguatera fish poisoning
- Paralytic shellfish poisoning
- Domoic acid poisoning
- Rabies
- Cholera
- Diarrhea of the Newborn (Outbreak)
- Any unusual diseases
- Outbreaks -any disease

** Potential bioterrorism agents*

† *MMWR Morb Mortal Wkly Rep. 2001 Oct 19;50(41):893-7.*

PREPARING FOR INFECTIOUS DISEASE EMERGENCIES

Community practitioners should be personally and professionally prepared to respond to a variety of infectious disease emergencies. The following are suggestions to help with this process.

FAMILY PLAN

Ensure that your family is well.

- ❑ Create and practice a family disaster plan. For more information see:
  - o SF OES, Household Family Plan: www.72hours.org
  - o Red Cross, Your Family Disaster Plan: www.prepare.org/basic/DisasterPlan.pdf
- ❑ Place fully stocked disaster kits in your home and car with a three-day supply of food and water.
  - o Red Cross, Emergency supply Kit Guide: www.prepare.org/basic/SuppliesKit.pdf
- ❑ Encourage staff to develop and practice family disaster plans.

CLINIC & OFFICE PLAN

Take steps to ensure the safety and well being of your staff. For suggestions and resources, see the *Clinic and Office Disaster & Emergency Planning* section in this *Guide.*

- ❑ Provide personal emergency kits and emergency contact numbers to staff.
- ❑ Make a telephone tree to notify staff in an emergency
- ❑ Develop and practice your clinic or office disaster and evacuation plan.
- ❑ Know the expected clinic/office emergency roles and responsibilities (including who assists patients and who will account for them when leaving the building).
- ❑ Know clinician roles and responsibilities in a community disaster. See the *Roles and Responsibilities* section.
- ❑ Identify items that should be taken in an evacuation (medicine, backup data, etc.)

EMERGENCY INFORMATION

Know where to obtain reliable San Francisco specific information.

- ❑ Visit and bookmark the Communicable Disease Control and Prevention website: **www.sfcdcp.org.**
- ❑ Register for Health Alerts. See instructions in the appendix.
- ❑ Note the radio stations that will provide emergency information:

KCBS 740 AM, KGO 810 AM, KNBR 680 AM, KQED 88.5 FM, KSJO 92.3 FM

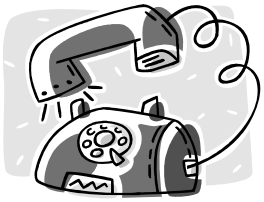
LEARN ABOUT INFECTIOUS DISEASE EMERGENCY

Know the details of infectious disease emergencies.

- ❑ Know what to report. See the *What to Report* section containing:
  - o List of diseases clinicians are legally required to report
  - o List of unusual conditions for which we request reports
- ❑ Review the potential bioterrorism related syndromes and the biological threat diseases (e.g., anthrax, avian influenza, botulism, brucellosis, plague, smallpox, tularemia, viral hemorrhagic fevers):
  - o See the Bioterrorism Syndromes poster
  - o See information in the *High Priority Diseases* section
- ❑ Maintain a reasonable index of suspicion
- ❑ Become knowledgeable and train staff on infection control measures. See *Infection Control Guidelines.*

REPORT TO SFDPH ON A ROUTINE BASIS

Routinely use components of your response plan. Informing SFDPH about diagnosed or suspected cases of reportable communicable diseases assists SFDPH disease control interventions and improves the ability to communicate with SFDPH in emergencies.



- ❑ Review and post:
  - o List of diseases clinicians are legally required to report
  - o List of unusual conditions for which we request reports
- ❑ Place SFDPH contact information in rolodex files
- ❑ Place SFDPH stickers on or near primary phones

CLINIC/OFFICE DISASTER & EMERGENCY PLANNING

Most health facilities in California (e.g., hospitals, long term care facilities, primary care clinics, adult day care centers) are required by state law to have a plan or program for addressing disasters. Medical offices are required to comply with local business ordinances including building and fire codes. It is also prudent for medical offices to develop disaster plans.

Several organizations have created documents to assist in the development of disaster plans. The California Office of Emergency Services (CA OES) and the California Primary Care Association have developed guidance and templates for clinic disaster plans.* The CDC and Red Cross provide guides for developing business disaster plans.*

Development and implementation of a disaster plan is divided into four phases:

1. **Hazard Mitigation**
2. **Preparedness**
3. **Response**
4. **Recovery**

You will find issues under each stage that need to be addressed in the development of your facility's disaster plan. Ideally plans should coordinate with neighborhood, local hospital, county and state partners.

SUGGESTED ITEMS TO INCLUDE IN A CLINIC OR OFFICE DISASTER PLAN

- ❑ Purpose of the disaster plan
- ❑ Scope of the disaster plan
- ❑ Plan activation
  - Who can active the plan
  - Circumstances when the plan should be activated.
- ❑ Disaster plan mission statement
- ❑ Leadership and succession leadership
- ❑ Delegation of authority
- ❑ Supporting plans and resources
- ❑ Legal authorities, codes, and policies
- ❑ Plan administration (e.g., distribution, updates)
- ❑ Staff activation and call down procedures
- ❑ Mutual aid agreements
- ❑ Communication procedures
- ❑ Organization chart
- ❑ Job action sheets

Specific plans

- ❑ Evacuation plan
- ❑ Transportation plan
- ❑ Medical management

* EMERGENCY PLAN RESOURCES

San Francisco Department of Emergency Management

- Homepage: www.sfgov.org/site/oes_index.asp
- How to prepare an emergency (family) plan: www.72hours.org

Red Cross, Family Disaster Plan Guidance, Emergency Supply Kit Guide, Workplace Preparedness:

- www.prepare.org

California Primary Care Association

- Clinic Disaster Plan Template: www.cpca.org/resources/cepp

California Office of Emergency Services, Clinic Disaster Plan Guide & Templates:

- www.oes.ca.gov/Operational/OESHome.nsf/ PDF/ClinicDisasGuide/$file/ClinicDisasGuide.pdf

CDC Emergency Preparedness For Business

- www.cdc.gov/niosh/topics/prepared

DISASTER PLAN DEVELOPMENT PHASES

The information described below on the phases of disaster plan development and implementation is adapted from the California Office of Emergency Service Clinic Disaster Plan Guidance from June 2002. (See url listed above for access to the complete document.)

Hazard Mitigation

Hazard mitigation will identify ways of minimizing future losses.

a. Hazard Vulnerability Analysis is the identification of hazards and the direct and indirect effect these hazards may have on the facility.

b. Structural Mitigation is reinforcing, bracing, anchoring, bolting, strengthening, or replacing any portion of the building that may become damaged and cause injury.

c. Nonstructural Mitigation reduces the threat to safety posed by the effects of earthquakes on such nonstructural elements as building contents, internal utility systems, interior glass and decorative architectural walls and ceilings. These actions involve identifying nonstructural fixtures and equipment, which are vulnerable to an earthquake and which are either essential to continued operations or a threat to public safety.

Preparedness

a. Disaster Plan. A well-written plan that has been tested will provide for an efficient systematic response to any type of a disaster or emergency.

b. Hazardous Materials Management - Internal and External. Clinics and/or offices may store and/or handle hazardous materials and the potential for these materials to be released is significant. Each clinic should identify these materials and develop procedures for safely handling, containing and neutralizing them. Staff training should include, but not be limited to, location of hazardous materials, safe handling, proper notification procedures, proper evacuation procedures, potential risks, storage, containment, neutralization, decontamination techniques and medical management of victims. Many Federal, State and local statutes, regulation and ordinances govern the handling and storage of hazardous materials. To determine the level of and need for compliance it is important that clinics or offices contact SFDPH Hazardous Materials Unified Program Agency at (415) 252-3900.

c. Weapons of Mass Destruction (WMD). Preparations for an event involving weapons of mass destruction – chemical, biological, nuclear, radiological or explosives (CBRNE) – begins with understanding the threat agents and the consequences of their use. This reference guide describes diseases potentially related to bioterrorism, appropriate initial responses and the roles and responsibilities of responders including community health care providers. Share the *Infectious Disease Emergencies Guide* with staff and place in a prominent and easily accessible location.

d. Managing Volunteers. Volunteers have a role in a disaster response but management of this resource is crucial.

e. Donations Management. Donations can quickly overwhelm a clinic especially when they are unsolicited. Coordination is accomplished by developing a plan prior to the emergency to handle receiving and distribution of the goods.

f. Training and Exercises. Training is achieved through exercising the clinic disaster plan without the stress of an actual disaster/emergency. This provides staff with the opportunity to become familiar with the plan and procedures, their roles and responsibilities, and the information and skills required to perform their duties during an emergency.

Response

a. Implementation of the Disaster Plan.

b. Organizational Chart. The organizational chart provides structure to a disaster or emergency response and features command, operations, planning and intelligence, logistics, and finance/administration positions. With small offices or clinics some functions may not be activated and/or some people may be responsible for more than one function.

c. Emergency Operation Center (EOC). The EOC is a key to successful response and recovery operations. It is the central location where all activities are coordinated. Coordination of activities will ensure that all tasks are accomplished with little or no duplication of effort.

Recovery

Clinics and offices should try to remain operational following an emergency. Planning can enable a more rapid and successful recovery or return to normal activities and minimize financial losses. Recovery issues to prepare for include: coping with structural and nonstructural damage to facilities, maintaining an inventory of damage and/or loss, accounting for lost revenue through disruption of services, personnel policies during and after an emergency, and meeting the psychological needs of staff and patients.

a. Financial Recovery Sources. In order to recover costs related to the disaster, complete documentation including photographs of damage is essential. Resources available to your facility during and after a major disaster could include:

- **Public Assistance (FEMA/OES)**
- **Small Business Administration (SBA)**
- **Federal Grant**
- **Insurance Carriers**

PERSONAL OFFICE DISASTER KIT

For the workplace, where you might be confined for several hours, or perhaps overnight, the following supplies are recommended. More information is at: www.redcross.org/services/disaster/beprepared.

❑ Flashlight with extra batteries

Use a flashlight if the power is out. Do not use candles or open flames.

❑ Battery-powered radio

News about the emergency may change rapidly as events unfold. Radio reports will give information about the areas most affected.

❑ Food

Enough non-perishable food to sustain you for at least one day, is suggested. Select foods that require no refrigeration, preparation or cooking, and little or no water. The following items are suggested:

- Ready-to-eat canned meals, meats, fruits, and vegetables.
- Canned juices.
- High-energy foods (granola/energy bars, etc.)

❑ Water

Keep at least one gallon of water available, or more if you are on medications that require water or that increase thirst.

❑ Medications

Include usual non-prescription medications that you take, including pain relievers, stomach remedies, etc.

If you use prescription medications, keep at least a three-day's supply of these medications at your workplace. Consult with your physician or pharmacist how these medications should be stored, and your employer about storage concerns.

❑ First Aid Supplies

Have the following essentials:

(20) Adhesive bandages, various sizes.
- (1) 5" x 9" sterile dressing.
- (1) Conforming roller gauze bandage.
- (2) Triangular bandages.
- (2) 3 x 3 Sterile gauze pads.
- (2) 4 x 4 Sterile gauze pads.
- (1) Roll 3" cohesive bandage.
- (2) Germicidal hand wipes or waterless alcohol-based hand sanitizer.
- (6) Antiseptic wipes.
- (2) Pair large medical grade non-latex gloves
- Adhesive tape, 2" width.
- Anti-bacterial ointment.
- Cold pack.
- Scissors (small, personal).
- Tweezers.
- CPR breathing barrier, such as a face shield

❑ Tools and Supplies

- Emergency "space" blanket (mylar).
- Paper plates and cups, plastic utensils.
- Non-electric can opener.
- Personal hygiene items, including a toothbrush, toothpaste, comb, brush, soap, contact lens supplies, and feminine supplies.
- Plastic garbage bags, ties (for personal sanitation uses).
- At least one complete change of clothing and footwear, including a long sleeved shirt and long pants, as well as closed-toed shoes or boots.
- If you wear glasses, keep an extra pair with your workplace disaster supplies.

❑ General Information

- Your kit should be adjusted based on your own personal needs.
- Do not include candles, weapons, toxic chemicals, or controlled drugs unless prescribed by a physician.

Excerpted from the American Red Cross Personal Workplace Disaster Supplies Kit

ANTHRAX

JULY 2008

Outline

Immediately report any suspected or confirmed cases of anthrax to:

SFDPH Communicable Disease Control
(24/7 Tel: 415-554-2830)

- By law, health care providers must report suspected or confirmed cases of anthrax to their local health department immediately [within 1 hr].
- SFDPH Communicable Disease Control can facilitate specialized testing and will initiate the public health response as needed.

Also notify your:

- Infection Control Professional
- Clinical Laboratory

INTRODUCTION

Anthrax is an acute infection caused by *Bacillus anthracis,* a large, gram-positive, spore-forming, aerobic, encapsulated, rod-shaped bacterium. Spores germinate and form bacteria in nutrient-rich environments, whereas bacteria form spores in nutrient-poor environments. The anthrax bacillus produces high levels of two toxins: Edema toxin causes massive edema at the site of germination, and lethal toxin leads to sepsis. Severity of anthrax disease depends on the route of infection and the presence of complications, with case-fatality ranging from 5% to 95% if untreated.[1-3]

The Working Group for Civilian Biodefense considers *B. anthracis* to be one of the most serious biological threats. Anthrax has been weaponized and used. It can be fairly easily disseminated and causes illness and death. Of the potential ways that *B. anthracis* could be used as a biological weapon, an aerosol release is expected to have the most severe medical and public health outcomes.[1]

EPIDEMIOLOGY

Anthrax as a Biological Weapon

Anthrax was successfully used as a biological weapon in the United States in October 2001. Cases resulted from direct or indirect exposure to mail that was deliberately contaminated with anthrax spores. In total, 22 cases were identified, 11 with inhalational (five fatal) and 11 with cutaneous anthrax (seven confirmed, four suspected).

Several countries have had anthrax weaponization programs in the past, including the United States. In 1979 an outbreak of anthrax in the Soviet Union resulted from accidental release of

anthrax spores from a facility producing weaponized anthrax. Of 77 reported human cases, all but two were inhalational, and there was an 86% fatality rate.[4]

Experts believe that an aerosol release of weapons-grade spores is the most likely mechanism for use of anthrax as a biological weapon in the future. Anthrax spores could also be used to deliberately contaminate food and water. Spores remain stable in water for several days and are not destroyed by pasteurization.[1]

An intentional release of anthrax may have the following characteristics:[1-3]

- Multiple similarly presenting cases *clustered in time*:
  - Severe acute febrile illness or febrile death
  - Severe sepsis not due to predisposing illness
  - Respiratory failure with a widened mediastinum on CXR
- Atypical host characteristics: unexpected, unexplained cases of acute illness in previously healthy persons who rapidly develop a progressive respiratory illness
- Multiple similarly presenting cases *clustered geographically*:
  - Acute febrile illness in persons who were in close proximity to a deliberate release of anthrax
- Absence of risk factors: patients lack anthrax exposure risk factors (e.g., veterinary or other animal handling work, meat processing, work that involves animal hides, hair, or bones, or agricultural work in areas with endemic anthrax)

Intentionally released anthrax spores may be altered for more efficient aerosolization and lethality (e.g., highly concentrated, treated to reduce clumping and reduce particle size, genetically modified to increase virulence, resist antimicrobials and reduce vaccine efficacy).

Naturally Occurring Anthrax

Reservoir

The natural reservoir for *B. anthracis* is soil, and the predominant hosts are herbivores (cattle, sheep, goats, horses, pigs, and others) that acquire infection from consuming contaminated soil or feed. Anthrax spores can persist in soil for years and are resistant to drying, heat, ultraviolet light, gamma radiation, and some disinfectants.[5] Anthrax in animals is endemic in many areas of the world and anthrax outbreaks in animals occur sporadically in the United States.

Mode of transmission

Anthrax is generally a zoonotic disease. Humans become infected through contact with infected animals and animal products through several mechanisms:[1, 5, 6]

- contact with infected animal tissues (e.g., veterinarians, animal handlers, meat processors, and other processes that involve animal hides, hair, and bones) or contaminated soil
- ingestion of contaminated, undercooked meat from infected animals
- inhalation of infectious aerosols (e.g., those generated during processing of animal products, such as tanning hides, processing wool or bone)

Person-to-person transmission of *B. anthracis* does not occur with gastrointestinal (GI) or inhalational anthrax, but has been reported rarely with cutaneous anthrax.[1]

Worldwide Occurrence

Worldwide, approximately 2000 cases are reported annually. Anthrax is more common in developing countries with less rigorous animal disease control programs. Cases of human anthrax are most often reported in South and Central America, Southern and Eastern Europe, Asia, Africa, the Caribbean, and the Middle East.[1] The largest reported outbreak of human anthrax occurred in Zimbabwe (1979-1985), which involved more than 10,000 individuals and was associated with anthrax disease in cattle.[2]

United States Occurrence

Naturally occurring anthrax is rare in the United States, with approximately 1-2 cases reported each year. The majority of anthrax cases in the United States are cutaneous and acquired occupationally in workers who come in contact with animals or animal products. Only 19 cases of naturally occurring inhalational anthrax have been reported since 1900, and there have been no confirmed gastrointestinal cases.[2, 7] Recent cases of naturally occurring anthrax include:

- In 2006, a New York City resident contracted inhalational anthrax while making drums from goat hides imported from Africa. The untanned hides were contaminated with anthrax spores, which may have been aerosolized during removal of hair.[7] The CDC believes that this was an isolated case and considers handling animal skins or making drums to be a low risk for cutaneous anthrax and extremely low risk for inhalational anthrax.[8]
- In 2002, two cases of cutaneous anthrax were reported. A laboratory worker from a Texas lab that processed environmental *B. anthracis* specimens contracted cutaneous anthrax through direct contact with a contaminated surface.[9] The second case occurred in a veterinarian who contracted the infection from a cow during necropsy.[10]
- Two cases of human cutaneous anthrax were reported following epizootics in North Dakota (2000) and southwest Texas (2001). Both cases resulted from exposure during disposal of infected animal carcasses.[11]

Occurrence in California and San Francisco

From 1994 to 2007, no cases of anthrax were reported in California.[12-15] However, in 2001 an outbreak of bovine anthrax caused the death of 21 beef cattle in a rural section of Santa Clara County.

CLINICAL FEATURES

There are three primary clinical types of anthrax disease, inhalational, cutaneous and gastrointestinal, which result from the way infection is acquired. Anthrax meningitis, which generally occurs as a complication of these primary forms of disease, is most likely to be seen with inhalational anthrax.

Anthrax infection is a severe clinical illness and can be life-threatening. Case fatality varies by the clinical type of disease. Overall case-fatality rates have declined because of more prompt administration of antibiotics and improved supportive care. Compared to historical rates, mortality has decreased from 86-95% to 45% for inhalational anthrax, 5-20% to less than 1% for cutaneous anthrax, and 25-60% to 12% for gastrointestinal anthrax. Anthrax meningitis case-fatality rates approach 95% even with antibiotic treatment.[2, 3, 16]

In the event of bioterrorism, the method of dissemination would influence the type of clinical disease that would be expected. Following an aerosol release, the majority of cases would be inhalational with some cutaneous cases whereas use of a small volume powder could result in both inhalational and cutaneous anthrax cases (as seen in the 2001 attacks). Gastrointestinal cases might occur following contamination of food or water.

Inhalational Anthrax

Inhalational anthrax is caused by inhalation of spores that reach the alveoli, undergo phagocytosis and travel to regional lymph nodes. The spores then germinate to become bacterial cells, which multiply in the lymphatic system and cause lymphadenitis of the mediastinal and peribronchial lymph nodes. The bacteria release toxins that cause hemorrhage, edema, and necrosis. Bacteria entering the bloodstream lead to septicemia, septic shock, and death. Systemic infection following inhalational anthrax is almost always fatal.[1]

One of the key clinical features of inhalational anthrax is evidence of pleural effusion and mediastinal widening on CXR or chest computed tomographic (CT) scan. Based on experience from the 2001 attacks, chest CT (without contrast) was found to be more sensitive than CXR for identification of mediastinal widening typical of inhalational anthrax.[3]

CLINICAL FEATURES: INHALATIONAL ANTHRAX[1, 2, 6, 17]	
Incubation Period	1-6 days (range <1 day to 8 weeks)
Transmission	Inhalation of aerosolized spores
Signs and Symptoms	• Initial presentation: Non-specific symptoms (low-grade fever, chills, nonproductive cough, malaise, fatigue, myalgias, profound sweats, chest discomfort) • Intermediate presentation: Abrupt onset of high fever, dyspnea, progressive respiratory distress, confusion, nausea or vomiting • Fulminant disease progression, if untreated
Progression and Complications	• Severe respiratory distress (dyspnea, stridor, cyanosis), which may be preceded by 1-3 days of improvement • Pleural effusions • Meningitis • Shock
Laboratory and Radiographic Findings	• Chest CT or radiograph: mediastinal widening (often), pleural effusions that are commonly hemorrhagic (often), infiltrates (rare) • Gram-positive bacilli on unspun peripheral blood smear or CSF • Elevated transaminases • Hypoxemia • Metabolic acidosis • Total WBC count normal or slightly elevated with elevated percentage of neutrophils or band forms
CSF, cerebrospinal fluid; WBC, white blood (cell) count.	

Cutaneous Anthrax

In cutaneous anthrax, spores or bacilli are introduced through cuts or breaks in the skin. Spores germinate at the site of contact and release toxins, causing development of a lesion and edema. Organisms may be carried to regional lymph nodes and cause painful lymphadenopathy and lymphangitis. Septicemic complications of cutaneous anthrax occur in 10-20% of untreated cases.[1-3]

CLINICAL FEATURES: CUTANEOUS ANTHRAX[1, 2, 6, 17]	
Incubation Period	3-4 days (range 1–12 days)
Transmission	• Direct skin contact with spores; in nature, contact with infected animals or animal products (usually related to occupational exposure) • Bite of infective arthropod (rare)
Signs and Symptoms	• Local skin involvement after direct contact with spores or bacilli (commonly seen on hands, forearms, head, and neck) • Skin lesion with the following progression: 1) Development of a papular lesion and localized itching, 2) papule turns into vesicular or bulbous lesion accompanied by painless edema, 3) lesion becomes necrotic and vesicles may surround the ulcer, and 4) lesion develops painless black eschar within 7–14 days of initial lesion • Lymphadenopathy and lymphangitis • Fever and malaise (common)
Progression and Complications	• Bacteremia • Meningitis • Extensive edema causing airway compression • Sepsis
Laboratory Findings	• Bacilli may be seen on Gram stain of subcutaneous tissue

Pediatric considerations: A case of cutaneous anthrax occurred in a 7-month old during the anthrax attack of 2001. This case was difficult to recognize and rapidly progressed to severe systemic illness despite timely antibiotic treatment. Clinical features included a painless draining lesion with edema that developed into an eschar, fever, leukocytosis, severe microangiopathic hemolytic anemia, renal failure, and coagulopathy.[18]

Gastrointestinal Anthrax

Gastrointestinal (GI) anthrax results from ingestion of *B. anthracis* bacteria, such as may be found in poorly cooked meat from infected animals. The incubation period for GI anthrax is 1-7 days. Two clinical presentations have been described: intestinal and oropharyngeal.

With *intestinal anthrax*, intestinal lesions occur in the ileum or cecum and are followed by regional lymphadenopathy. Symptoms of intestinal anthrax are initially nonspecific and include low-grade fever, malaise, nausea, vomiting, anorexia and fever. As disease progresses, abdominal pain, hematemesis, and bloody diarrhea develop. The patient may present with findings of an acute abdomen. After 2-4 days, ascites develop and abdominal pain lessens. Hematogenous spread with

resultant septicemia can occur. Mesenteric adenopathy on CT scan is likely, and mediastinal widening on CXR is possible.[1, 2, 5, 6]

In *oropharyngeal anthrax*, a mucosal ulcer occurs initially in the mouth or throat, associated with fever, throat pain, and dysphasia. This is followed by cervical edema and regional lymphadenopathy. Ulcers may become necrotic with development of a white patch covering the ulcer. Swelling can become severe enough to affect breathing. Hematogenous spread, septicemia, and meningitis can occur.[1, 2, 5, 6]

Gram stain of ascitic fluid, oropharyngeal ulcers, or unspun peripheral blood may show Gram-positive rods. Leukocytosis with left shift may be present. *B. anthracis* can be cultured from oropharyngeal swabs and stool specimens.[6]

Anthrax Meningitis

Anthrax meningitis can occur as a complication of cutaneous, inhalational, or GI anthrax, but is most commonly seen with inhalational anthrax (up to 50%). Patients may or may not present with symptoms of the primary site of infection. In addition to typical symptoms of bacterial meningitis, anthrax meningitis may involve hemorrhage or meningoencephalitis. Case fatality with anthrax meningitis is greater than 90%. Even one case of anthrax meningitis should alert public health authorities to identify the source of exposure and investigate the possibility of bioterrorism.[3]

Anthrax and Pregnant Women

Maternal and perinatel complications are not completely understood, because anthrax infection during pregnancy is rare. Preterm delivery may be one of the major complications.[19]

DIFFERENTIAL DIAGNOSIS

Because of its mild, nonspecific nature in the early states, a high index of suspicion is necessary to make a timely diagnosis of anthrax. Screening protocols and clinical prediction tools have been proposed and partially evaluated.[20] Prompt administration of antibiotics can be critical to patient survival; therefore, clinicians should administer appropriate antibiotics when the diagnosis is suspected.[1]

Differential: Inhalational Anthrax[1, 2, 5, 6, 21]

Early disease mimics influenza and other respiratory infections. However nasal symptoms are typically not present and rapid diagnostic tests, such as nasopharyngeal swabs for detection of respiratory virus antigens, would typically be negative.

Key features that distinguish *inhalational* anthrax from other conditions are:

- CXR is abnormal even during early stages of influenza like illness
- CXR or chest CT show widened mediastinum and pleural effusion but minimal or no pneumonitis

Features that distinguish *inhalational* anthrax from influenza:

- Neurological symptoms without headache (e.g., confusion, syncope) and nausea/vomiting are more common in inhalational anthrax
- Rhinorrhea and pharyngitis were uncommon in inhalational anthrax cases from 2001 U.S. attack

Other conditions to consider are:

- bacterial pneumonia (*Mycoplasma, Staphylococcus, Streptococcus, Haemophilus, Klebsiella, Moraxella, Legionella)*
- *Chlamydia* infection
- influenza
- other viral pneumonia (respiratory syncytial virus [RSV], cytomegalovirus [CMV], hantavirus)
- Q fever
- pneumonic plague
- tularemia
- primary mediastinitis
- ruptured aortic aneurysm
- histoplasmosis
- coccidiodomycosis
- silicosis
- sarcoidosis

Differential: Cutaneous Anthrax[3, 5, 6]

Key features that distinguish *cutaneous* anthrax are:

- painlessness of the lesion itself
- large extent of local edema

Other conditions to consider:

- ecthyma gangrenosum
- ulceroglandular tularemia
- bubonic plague
- cellulitis (staphylococcal or streptococcal)
- brown recluse spider bite
- necrotizing soft tissue infections, (e.g., *Streptococcus*, *Clostridium*)
- Coumadin or heparin necrosis
- rickettsial infection
- necrotic herpes simplex infection
- orf virus infection
- glanders
- cutaneous leishmaniasis
- cat scratch fever
- melioidosis

Differential: Gastrointestinal Anthrax[2, 5]

The differential diagnosis for the *intestinal* form of the disease includes:

- typhoid fever
- intestinal tularemia
- acute bacterial gastroenteritis (e.g., *Campylobacter, Shigella*, toxicogenic *Escherichia coli, Yersinia*)
- bacterial peritonitis
- peptic or duodenal ulcer
- any other causes of acute abdomen

The differential diagnosis for the *oropharyngeal* form of the disease includes:

- streptococcal pharyngitis
- infectious mononucleosis
- diphtheria
- pharyngeal tularemia
- other causes of pharyngitis (e.g., enteroviral vesicular, herpetic, anaerobic or Vincent's angina, *Yersinia enterocolitica)*

Differential: Anthrax Meningitis[3, 5]

A key feature that distinguishes anthrax meningitis is bloody cerebrospinal fluid (CSF) containing gram-positive bacilli.

Other conditions to consider are:

- subarachnoid hemorrhage
- bacterial meningitis
- aseptic meningitis

LABORATORY AND RADIOGRAPHIC FINDINGS

The diagnosis of anthrax requires a high index of suspicion because the disease often presents with nonspecific symptoms. Routine laboratory and radiographic findings for specific clinical presentations of anthrax are listed in the clinical features tables.

If you are testing or considering testing for anthrax, you should:

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830).** SFDPH can authorize and facilitate testing, and will initiate the public health response as needed.
- **Inform your lab that anthrax is under suspicion. Labs may view Gram-positive bacilli as contaminants and may not pursue further identification unless notified.**

Initial identification and diagnosis of the organism relies on evaluation of infected tissue (blood, sputum, CSF, fluid collected from an unroofed vesicle, ulcer, eschar, or skin lesion scraping, or stool). The gold standard for anthrax diagnosis is direct culture of clinical specimens onto blood agar with demonstration of typical Gram stain, motility, and biochemical features. Blood cultures, which are positive nearly 100% of the time in inhalational anthrax, should be obtained prior to antibiotic administration because there is rapid sterilization of blood after a single dose of antibiotics. Because laboratories may view gram-positive bacilli as contaminants and because *B. anthracis* may be a risk to laboratory personnel, clinicians should notify the laboratory when anthrax is suspected.[1-3, 5]

Although rapid diagnostic tests are not widely available, the public health laboratory system may be able to provide this testing on clinical specimens. Other tests available through the public health

laboratory system include polymerase chain reaction (PCR), serologic tests, and immunohistochemistry.[22]

Testing for Exposure to aerosolized Anthrax

Nasal swab cultures have been used to study environmental exposure to aerosolized anthrax, they are not recommended for use in the clinical setting. The sensitivity, specificity, and predictive value of nasal swab cultures is not known.[6]

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfcdcp.org).

Treatment of Confirmed or Suspected Anthrax

This section refers to individuals with suspected or confirmed anthrax disease.

The basic components of treatment for anthrax consist of hospitalization with intensive supportive care and IV antibiotics. After obtaining appropriate cultures, antimicrobials should be started *immediately* on suspicion and prior to confirmation of the diagnosis.[1] Patients with inhalational anthrax who received antibiotics within 4.7 days of exposure had a 40% case fatality, compared to a 75% case-fatality in those with treatment initiated after 4.7 days.[21]

Because susceptibility data will be delayed, initial antibiotics must be chosen empirically. Recommendations for initial empiric therapy of suspected or confirmed anthrax disease are described below. Empiric therapy with at least two agents is recommended because of the potential for infection with strains of *B. anthracis* engineered to be penicillin- and/or tetracycline-resistant.[1] Antibiotic resistance to amoxicillin is of greater concern than resistance to doxycycline or ciprofloxacin; therefore, amoxicillin is not recommended as a first-line agent unless the strain has been proven susceptible. Therapy may be switched to oral antimicrobials when clinically indicated. Therapy should be continued for a total duration of 60 days because spores can persist and then germinate for prolonged periods. There is a possibility that spores could germinate and cause illness up to 100 days after exposure.[1]

Contained casualty setting: Parenteral antimicrobial therapy with at least two agents is recommended for *inhalational and GI anthrax* when individual medical management is available. After clinical improvement is noted, treatment can be switched to oral therapy with ciprofloxacin or doxycycline, based on susceptibilities and clinical considerations. Draining of pleural effusions has also been associated with reduced mortality.[21]

Cutaneous anthrax can be treated with oral antibiotics. If in addition to cutaneous lesions there are signs of systemic disease or extensive edema, or if lesions are present on the head or the neck, then the multidrug IV regimen is recommended.

ANTHRAX: TREATMENT AND POST-EXPOSURE PROPHYLAXIS RECOMMENDATIONS[A]

	INITIAL IV THERAPY[B,C] FOR INHALATIONAL, GI ANTHRAX, OR CUTANEOUS ANTHRAX WITH COMPLICATIONS[D]	INITIAL THERAPY FOR CUTANEOUS ANTHRAX[B,D]	THERAPY FOR ANTHRAX IN THE MASS CASUALTY SETTING, OR POSTEXPOSURE PROPHYLAXIS, OR AFTER CLINICAL IMPROVEMENT ON IV THERAPY[E,F]
Adult	**Ciprofloxacin,** 400 mg IV q12 hr **or** **Doxycycline**[G]**,** 100 mg IV q12 hr **AND** One or two additional antimicrobials (agents with *in vitro* activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin)[H]	**Ciprofloxacin**, 500 mg orally q12 hrs for 60 days ***or*** **Doxycycline**, 100 mg orally q12 hrs for 60 days	**Ciprofloxacin**[I], 500 mg orally twice daily for 60 days **or** **Doxycycline**[J], 100 mg orally twice daily for 60 days
Children	**Ciprofloxacin**[K,L], 10 mg/kg IV q12 hrs (max 400 g/dose) **or** **Doxycycline:**[G,L,M] ≥45 kg, 100 mg IV q12 hr <45 kg, give 2.2 mg/kg IV q12 hrs (max 200 mg/day) **AND** One or two additional antimicrobials (agents with *in vitro* activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin)[H]	**Ciprofloxacin**, 15 mg/kg orally q12 hrs (max 500 mg/dose) for 60 days **or** **Doxycycline:**[G,L,M] ≥45 kg, give 100 mg orally q12 hrs for 60 days <45 kg, give 2.2 mg/kg orally q12 hrs (max 200 mg/day) for 60 days	**Ciprofloxacin**[I], 15 mg/kg orally twice daily (max 500 mg/dose) for 60 days **or** **Doxycycline**[J]: ≥45 kg, give 100 mg orally twice daily for 60 days <45 kg, give 2.2 mg/kg orally twice daily (max 200 mg/day) for 60 days **or** **Amoxicillin**[N] >20 kg: 500 mg orally three times daily for 60 days ≤20 kg: 80 mg/kg/day orally in three divided doses every 8 hrs for 60 days
Pregnant women	Same as for non-pregnant adults[O]	Same as for non-pregnant adults[O]	Same as for non-pregnant adults ***or*** **Amoxicillin**[N] 500 mg orally three times daily for 60 days
Immuno-compromised Persons	Same as for non-immunocompromised persons and children	Same as for non-immunocompromised persons and children	Same as for non-immunocompromised persons and children

[A] The treatment recommendations included in this table are adapted from guidance developed during the 2001 anthrax outbreaks. Therapy recommendations in other situations should be guided by antimicrobial susceptibility results.[1, 2, 6, 17]
[B] Ciprofloxacin or doxycycline should be considered an essential part of first-line therapy for inhalational anthrax.
[C] Steroids may be considered an adjunct therapy for patients with severe edema and for meningitis based on experience with bacterial meningitis of other etiologies.
[D] Cutaneous anthrax cases with signs of systemic involvement, extensive edema, or lesions on the head or neck require intravenous therapy, and a multidrug approach is recommended.
[E] Initial therapy may be altered based on clinical course of patient; one or two antimicrobial agents (eg, ciprofloxacin or doxycycline) may be adequate as patient improves.
[F] If pharmaceutical resources permit in a mass casualty setting, therapy with at least two agents is recommended over monotherapy.
[G] If meningitis is suspected, doxycycline may be less optimal because of poor central nervous system penetration.
[H] Because of concerns of constitutive and inducible beta-lactamases in *Bacillus anthracis* isolates, penicillin and ampicillin should not be used alone. Consultation with an infectious disease specialist is advised.
[I] In vitro studies suggest that ofloxacin (400 mg orally every 12 hours) or levafloxacin, (500 mg orally every 24 hours) could be used in place of ciprofloxacin – if supplies were limited in a mass casualty or post-exposure prophylaxis situation. FDA has approved levafloxacin for PEP in adults and children.
[J] In vitro studies suggest that 500 mg of tetracycline orally every 6 hours could be used in place of doxycycline – if supplies were limited in a mass casualty or post-exposure prophylaxis situation.
[K] If intravenous ciprofloxacin is not available, oral ciprofloxacin may be acceptable because it is rapidly and well absorbed from the gastrointestinal tract with no substantial loss by first-pass metabolism. Maximum serum concentrations are attained 1-2 hours after oral dosing but may not be achieved if vomiting or ileus is present.
[L] Tetracycline and quinolone antibiotics are generally not recommended during pregnancy or childhood; however their use may be indicated for life-threatening illness. Ciprofloxacin may be preferred in pregnant women and children up to 8 years of age because of the known adverse event profile of doxycycline (e.g., tooth discoloration). Doxycycline may be preferred in children 8 years and older because of the adverse event profile of ciprofloxacin (e.g., arthropathies).
[M] American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (eg, Rocky Mountain spotted fever).
[N] Amoxicillin is not approved by the FDA for post-exposure prophylaxis or treatment of anthrax. However, CDC has indicated that if the isolate is determined to be susceptible to amoxicillin, it could be used for pregnant women and children for post-exposure prophylaxis or for completion of 60 days antibiotic therapy after initial treatment with ciprofloxacin or doxycycline. Amoxicillin resistance to anthrax is of greater concern than that of doxycycline or ciprofloxacin, and amoxicillin is not recommended as a first-line agent unless the isolate is proven to be susceptible.
[O] Although tetracyclines are not recommended for pregnant women, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dose-related; therefore, doxycycline might be used for a short time (7-14 days) before 6 months of gestation.

Anthrax meningitis can be treated using the inhalational anthrax guidelines; however, IV treatment with a fluoroquinolone plus 1-2 antimicrobials with good central nervous system (CNS) penetration

and activity against *B. anthracis* (i.e., rifampin, vancomycin, penicillin, ampicillin, meropenem) is recommended. The addition of corticosteroids may help manage cerebral edema.[23]

Mass casualty setting: Use of oral antibiotics may be necessary if the number of patients exceeds the medical care capacity for individual medical management. If pharmaceutical resources permit, therapy with at least two agents is recommended over monotherapy.

Prophylaxis of Persons Exposed but Without Symptoms

Postexposure prophylaxis (PEP) is the administration of antibiotics, with or without vaccine, after suspected exposure to anthrax has occurred but before symptoms are present. (If symptoms are present, see section on treatment, above). In general, PEP is recommended for persons exposed to an air space or package contaminated with *B. anthracis*. Unvaccinated laboratory workers exposed to *B. anthracis* cultures should also receive PEP.[1] As there is no known person to person transmission of inhalational anthrax, prophylaxis should not be offered to contacts of cases, unless also exposed to the original source.[1]

Postexposure prophylaxis of potential inhalational anthrax consists of oral administration of either ciprofloxacin or doxycycline. Therapy should be continued for 60 days. Patients treated for exposure should be informed of the importance of completing the full course of antibiotic prophylaxis regardless of the absence of symptoms.[1, 22, 24] The Food and Drug Administration (FDA) has also approved levafloxacin and penicillin G procaine for PEP of inhalational anthrax. .[25] And levafloxacin was approved recently for children older than 6 months.[26] Because of concerns about use of doxycycline or ciprofloxacin in children and about doxycycline use in pregnant women, the CDC has indicated that for prophylaxis, therapy can be switched to amoxicillin in these groups if the isolate is determined to be susceptible. Amoxicillin may also be considered for patients allergic to both ciprofloxacin and doxycycline.[1, 22, 24]

The Advisory Committee on Immunization Practices recommends the use of combined antimicrobial prophylaxis and vaccine [Biothrax (formerly Anthrax vaccine absorbed, AVA)]. Biothrax is not licensed for this use by the FDA, and would need to be given under an Investigational New Drug (IND) application. The recommended regimen is three vaccine doses (given at 0, 2, and 4 weeks after exposure) and at least a 30-day course of antimicrobial therapy. The CDC does not recommend vaccination in pregnant women given lack of data.[27]

Following the 2001 attacks, exposed persons were given the option of (1) 60 days of antibiotic prophylaxis; (2) 100 days of antibiotic prophylaxis, and (3) 100 days of antibiotic prophylaxis, plus anthrax vaccine (under IND protocol).[28]

Anthrax Vaccine

The anthrax vaccine Biothrax (formerly Anthrax vaccine absorbed, AVA) is available but only in limited supply that is controlled by federal authorities. It is an inactivated cell-free filtrate of an avirulent strain of *B. anthracis.* Local reactions and mild systemic reactions are common. Severe allergic reactions are rare (<1 per 100,000).[1, 27]

The anthrax vaccine is licensed for pre-exposure use to prevent cutaneous anthrax in healthy, nonpregnant adults 18-65 years of age who have a high likelihood of coming into contact with anthrax, including certain laboratory workers and animal processing workers. AVA is not currently licensed for postexposure use and must be given in this context under an FDA investigational drug protocol. The CDC may recommend its use for PEP under some circumstances. Research is underway on new anthrax vaccines.[1, 27]

Developmental Anthrax Therapeutics

Additional therapeutic candidates for treatment and prophylaxis of anthrax are currently under development. The Department of Health and Human Services announced plans to purchase the antibody-based therapeutic candidates immune globulin (AIG) and ABthrax™ (raxibacumab) for the strategic national stockpile. These therapeutic approaches use antibodies to neutralize anthrax toxin. Neither AIG nor ABthrax™ is FDA approved, but either may be authorized for use as an investigational new drug in an emergency. Studies are still in progress to determine efficacy of these therapeutics in anthrax treatment and prophylaxis.[6]

COMPLICATIONS AND ADMISSION CRITERIA

Without early antibiotic treatment, inhalational anthrax progresses to pneumonitis marked by severe respiratory distress and cyanosis, and is often accompanied by pleural effusion. Patients with anthrax pneumonitis are particularly likely to develop septicemia and septic shock due to hematogenous dissemination of the bacteria. Sepsis may also develop as a complication of cutaneous anthrax or gastrointestinal anthrax. Anthrax meningitis may occur as a consequence of hematogenous dissemination.

Patients with suspected or confirmed inhalational, gastrointestinal, or meningeal anthrax, as well as those with cutaneous anthrax who exhibit head or neck lesions, extensive edema, or systemic signs of illness, require admission for intravenous antibiotic therapy and supportive care.

INFECTION CONTROL

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfcdcp.org).

Clinicians should notify local public health authorities, their institution's infection control professional, and their laboratory of any suspected anthrax cases. Public health authorities may conduct epidemiologic investigations and implement disease control interventions to protect the public. Both HICPAC (Hospital Infection Control Practices Advisory Committee) of the CDC and the Working Group for Civilian Biodefense recommend **Standard Precautions** for anthrax patients in a hospital setting without the need for isolation. Person to person transmission has only rarely been reported for patients with cutaneous anthrax and **Standard Precautions** are considered adequate. Routine laboratory procedures should be carried out under Biosafety Level 2 (BSL-2) conditions.[1, 29]

Decontamination

Contaminated surfaces can be disinfected with commercially available bleach or a 1:10 dilution of household bleach and water. All persons exposed to an aerosol containing *B. anthracis* should be instructed to wash body surfaces and clothing with soap and water.[1]

PEARLS AND PITFALLS

- The initial (prodromal) phase of inhalational anthrax resembles an influenza-like syndrome and can be difficult to distinguish from seasonal respiratory illnesses. Nasal congestion and rhinorrhea, however, are common features of seasonal influenza-like syndromes and are unusual with pulmonary anthrax.

- The classic radiographic findings of inhalational anthrax – CXR showing a widened mediastinum (due to hilar lymphadenopathy) and pulmonary effusion – although not unique to anthrax, should nonetheless prompt a high level of clinical suspicion.

- The necrotic, edematous, eschar-covered skin lesion of cutaneous anthrax is usually painless, which is an important differentiating feature from a brown recluse spider bite.

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AVIAN INFLUENZA

AUGUST 2005

Outline

Influenza A is not a reportable condition under Calif. law. However, health care providers are required to report any UNUSUAL disease to the local health department within one hour.

In the event of Avian Influenza outbreak, SFDPH will issue guidelines for case identification, infection control, and disease reporting, at www.sfdph.org/cdcp.

SFDPH communicable disease control may be contacted by phone at 415-554-2830.

AGENT

Influenza virus belongs to the Orthomyxovirus family and contains 8 different segments of negative-stranded RNA. There are 3 types: A, B, and C, distinguishable by internal virus proteins. Influenza A is responsible for most human influenza disease, causes avian influenza, and is the source of all past influenza pandemics in humans. Influenza B is a disease of humans only, while inluenza C causes milder illness in both humans and swine and occurs uncommonly.

Influenza A is subtyped based on viral envelope glycoproteins hemagglutinin (HA) and neuraminidase (NA). There are 16 different HA antigens (H1 to H16) and 9 different NA antigens (N1 to N9) for influenza A. Human disease has historically been related to 3 subtypes of HA (H1, H2, and H3) and 2 subtypes of NA (N1 and N2).

Influenza A infects humans, birds, pigs, horses, whales, seals, and has recently been recognized in felines. Avian influenza A can infect a variety of domestic and wild bird species. Avian influenza in domestic chickens and turkeys is classified according to disease severity, with two recognized forms: highly pathogenic avian influenza (HPAI), and low-pathogenic avian influenza (LPAI). Avian influenza viruses that cause HPAI are highly virulent and mortality rates in infected flocks often approach 100%. All known subtypes of influenza A can be found in birds, but only subtypes H5 and H7 have caused HPAI outbreaks.

EPIDEMIOLOGY

Influenza Pandemics

Pandemics differ from seasonal outbreaks or "epidemics" of influenza, which are caused by subtypes of influenza viruses that already exist among people. A pandemic is a global outbreak that occurs when a new, highly pathogenic strain of influenza type A virus emerges in the human population and spreads easily from person-to-person worldwide, aided by the lack of human immunity to the novel strain.

Past influenza pandemics have led to high levels of illness, death, social disruption, and economic loss. There were 3 influenza A pandemics during the 20th century:

- 1918-19, "Spanish flu," (H1N1), caused >500,000 deaths in the USA and >50,000,000 deaths worldwide. Nearly half of those who died were young, healthy adults.
- 1957-58, "Asian flu," (H2N2), first identified in China in early 1957, it caused about 70,000 deaths in the USA by June 1957.
- 1968-69, "Hong Kong flu," (H3N2), caused about 34,000 deaths in the United States. Influenza A (H3N2) viruses still circulate today.

Influenza in Bird Populations

All birds are believed susceptible to infection with avian influenza. Migratory waterfowl – most notably wild ducks – are the natural reservoir of avian influenza viruses, however domestic poultry, including chickens and turkeys, are particularly susceptible to epidemics of rapidly fatal influenza.

Recent research has shown that viruses of low pathogenicity can quickly mutate into highly pathogenic viruses. For example, during a 1999–2001 avian influenza epidemic in Italy, the H7N1 virus, initially of low pathogenicity, mutated within 9 months to a highly pathogenic form. More than 13 million birds died or were destroyed.

Standard control measures aimed at preventing spread of HPAI in a country's poultry population include quarantining of infected farms and destruction of infected or potentially exposed flocks.

In the absence of prompt control measures backed by good surveillance, epidemics can last for years. For example, an epidemic of H5N2 avian influenza, which began in Mexico in 1992, started with low pathogenicity, evolved to the highly fatal form, and was not controlled until 1995.

Mechanism of Transmission to Humans

Influenza A viruses are genetically labile and well adapted to elude host defenses. Influenza viruses lack mechanisms for the "proofreading" and repair of errors that occur during replication. As a result of these uncorrected errors, the genetic composition of a virus changes during passage through humans and animals, and the existing strain is replaced with a new antigenic variant. These changes in the antigenic composition of influenza A viruses are known as antigenic drift.

Influenza A viruses, including subtypes from different species, can also swap or reassort genetic materials. This process -- known as antigenic shift – creates a novel virus subtype that differs genetically from both parent viruses. As populations will have no immunity to the new subtype, and as no existing vaccines can confer protection, antigenic shift has historically resulted in highly lethal pandemics. For this to happen, a subtype of avian influenza needs to acquire genes from human influenza viruses that enable person-to-person transmission.

Conditions favorable for the emergence of antigenic shift are thought to involve humans living in close proximity to domestic poultry and pigs. Because pigs are susceptible to infection with both avian and mammalian viruses, including human strains, they can serve as a "mixing vessel" for the scrambling of genetic material from human and avian viruses, resulting in the emergence of a novel subtype. In addition, evidence is mounting that, for at least some avian influenza virus subtypes circulating in bird populations, humans themselves can serve as the "mixing vessel".

The Current H5N1 Threat

Of the avian influenza subtypes, currently the H5N1 subtype is of greatest pandemic concern for the following reasons:

- Rapid spread throughout poultry flocks in Asia; now appears to be endemic in eastern Asia
- Mutates rapidly
- Propensity to acquire genes from viruses infecting other animal species
- Causes severe disease in humans, with a high case-fatality rate (approx. 70%)
- There is ongoing exposure and infection of humans in rural Asia, where many households keep free-ranging poultry flocks for income and food

The first documented infection of humans with an avian influenza virus occurred in Hong Kong in 1997, when the H5N1 strain caused severe respiratory disease in 18 humans, of whom 6 died. The infection of humans coincided with an epidemic of HPAI, caused by the same strain, in Hong Kong's poultry population. Close contact with live infected poultry was the source of human infection, and the virus was shown to have jumped directly from birds to humans. Transmission to health care workers occurred, but did not cause severe disease. Rapid destruction of Hong Kong's entire poultry population, estimated at around 1.5 million birds, reduced opportunities for further direct transmission to humans, and may have averted a pandemic.

Alarms have continued to mount since 2003, when an outbreak of HPAI caused by the H5N1 strain spread rapidly through poultry farms in southeastern Asia. Areas currently affected by H5N1 avian influenza in poultry include Cambodia, China (both Taiwan and the People's Republic of China), Hong Kong, Indonesia, Japan, Laos, Malaysia, Philippines, South Korea, Thailand, and Vietnam. Over 140 million chickens have been slaughtered to halt spread of the virus.

The strain circulating in Asia appears highly pathogenic for humans, and immunity in the human population is generally lacking. If H5N1 continues to circulate widely among poultry, the potential

for emergence of a pandemic strain remains high. Human cases of H5N1 have been reported officially in Vietnam, Thailand, and Cambodia. Between December 26, 2003 and June 28, 2005, the WHO has tallied 108 laboratory-confirmed cases of H5N1 influenza in humans (54 of them fatal). Probable person-to-person transmission was identified in Thailand involving transmission from an ill child to her mother and aunt. However, the strain has not yet been shown to be easily transmitted between humans, and sustained person-to-person transmission has not occurred.

CLINICAL FEATURES

Typical clinical features of influenza A are shown in the following table.

INFLUENZA A: CLINICAL FEAURES	
Incubation Period	1-2 days
Signs & Symptoms	Initially, systemic symptoms predominate • Fever (duration 3 days, range 2-8 days) • Chills, malaise, headache, myalgias, arthralgias, anorexia, toxic appearance, occasionally prostration • Dry cough, pharyngeal pain, rhinorrhea Convalescent period lasts 1-3 weeks • Cough, lassitude, and malaise
Complications	• Primary influenza pneumonia; rapid progression of fever, cough, dyspnea, cyanosis • Secondary bacterial pneumonia • Croup • Exacerbation of COPD • Myositis; myoglobinuria • Myocarditis; pericarditis • Toxic shock syndrome • Encephalitis (rare)
Laboratory Findings	• WBC often normal (unless secondary bacterial process: elevated with left shift) • Sputum gram stain unremarkable (unless secondary bacterial pneumonia) • CXR usually normal in uncomplicated influenza; usually shows infiltrates and/or consolidation when pneumonia present

In an outbreak of avian influenza among humans, the clinical picture of primary viral pneumonia may predominate. However given that the virus responsible for human-to-human transmission will be a novel strain, the specifics of its clinical presentation will not be known until the outbreak actually occurs. A recent report of avian influenza A (H5N1) in 10 patients in Vietnam demonstrated the following clinical features of the illness:

- Incubation period was 2-4 days (mean 3 days)
- 10/10 presented with fever, shortness of breath, and cough

- 5/10 reported sputum production; in 3 of these, sputum was blood-tinged.
- 7/10 reported diarrhea.
- None complained of sore throat, conjunctivitis, rash, or a runny nose.
- 10/10 had abnormal CXR at the time of hospital admission (including extensive bilateral infiltration, lobar collapse, focal consolidation, and air bronchograms).
- 10/10 had lymphopenia, and 9/10 had thrombocytopenia at presentation
- 10/10 received broad-spectrum antibiotics
- 5/10 were treated with oseltamivir (4 of whom died)
- 8/10 died

A recent case report of a 4-year-old Vietnamese child with H5N1 avian influenza who presented in 2004 with encephalitis demonstrated the following features:

- The child presented with a 2-day history of fever, headache, vomiting, and severe diarrhea
- Laboratory tests on admission were unremarkable and chest x-ray was normal.
- On day 3, the child had a generalized convulsion and became comatose. He developed respiratory failure and died on day 5.
- H5N1 influenza A virus was isolated from CSF, fecal, throat, and serum specimens.
- Acute encephalitis was reported as the cause of death

SURVEILLANCE AND DIAGNOSIS

As of this writing, CDC recommendations issued February 2004 (and re-affirmed February, 2005) for enhanced surveillance of patients at risk for avian influenza are still in effect. These are:

If you consider testing for Avian Influenza, you should:

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830) to facilitate testing and initiate the public health response. Testing for H5N1 subtype of influenza A occurs as specialized labs and requires SFDPH authorization.**
- **Inform your laboratory that Avian Influenza is under suspicion, so that they may follow the appropriate biosafety procedures.**

1) Testing for influenza A(H5N1) in the USA is indicated for hospitalized patients with:

- Radiographically confirmed pneumonia, acute respiratory distress syndrome (ARDS), or other severe respiratory illness for which an alternate diagnosis has not been established, AND
- History of travel within 10 days of symptom onset to a country with documented H5N1 avian influenza in poultry and/or humans. (List of H5N1-affected countries available at www.who.int/topics/avian_influenza)

2) Testing for influenza A(H5N1) should be considered on a case-by-case basis in consultation with the local health department for hospitalized or ambulatory patients with:

- Documented temperature of >38°C (>100.4°F), AND

- At least one: cough, sore throat, shortness of breath, AND
- History of contact with domestic poultry (e.g., visited a poultry farm, household raising poultry, or bird market) or a known or suspected human case of influenza A(H5N1) in an H5N1-affected country within 10 days of symptom onset.

Clinical specimens from suspect influenza A(H5N1) cases may be tested by PCR assays under strict biosafety precautions at public health reference laboratories. Virus isolation studies carry higher risks of inadvertent transmission and require even more stringent precautions.

TREATMENT AND PROPHYLAXIS

Detailed guidelines for Avian Influenza treatment/prophylaxis have not yet been issued. For updates and situational guidance in response to events, check www.sfdph.org/cdcp.

Antiviral Agents

There are 2 key uncertainties that challenge planning for administration of antiviral agents in the event of an avian influenza outbreak among humans. First, it is unclear how much antiviral drug will be available in the event of a large-scale outbreak. Second, the influenza strain responsible for the outbreak and its profile of antibiotic resistance may not be fully known in advance.

There are 2 classes of antiviral agents for influenza: adamantanes (amantadine and rimantadine), and neuraminidase inhibitors (zanamivir and oseltamivir). The drugs differ in cost, routes of administration, adverse events, contraindications, and potential for antiviral resistance.

CHARACTERISTICS OF ANTI-INFLUENZA ANTIVIRAL AGENTS

	Adamantane Derivatives		Neuraminidase Inhibitors	
	Amantadine	**Rimantadine**	**Oseltamivir**	**Zanamivir**
Route	Oral	Oral	Oral	Inhalation
Treatment License	≥1 year old	>1 year old	≥13 years old	Not FDA Approved
Prophylaxis License	≥1 year old	Adults	≥1 year old	≥7 years old
Selected Adverse Events	CNS (dizziness, insomnia, seizures, suicidality); GI (nausea); some reports cardiac toxicity	CNS (e.g. insomnia, dizziness), GI (e.g. nausea, vomiting)	GI (principally nausea, vomiting)	Poss. bronchospasm and decrease in lung function, esp. in patients with underlying airway disease

Adapted from: DHHS Pandemic Influenza Response & Preparedness Plan, Aug. 26, 2004

Both classes of drugs reduce duration of uncomplicated influenza when started within 2 days of illness onset. However, there are no controlled studies of patients infected with influenza A(H5N1).

Vaccine Development

Influenza vaccine must be both subtype- and strain-specific. Candidate vaccines against H5N1 subtype were developed during 2003 for protection against the strain that was isolated from humans in Hong Kong in February of that year. However, the current strain is different. Clinical trials of additional candidate H5N1 vaccines are currently under way. However, it is not clear if prototype H5 vaccines will offer protection against an emergent pandemic strain, and WHO has indicated that 4-6 months (minimum) would be needed to develop a vaccine against a novel strain.

INFECTION CONTROL*

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfdph.org/cdcp).

Poultry Workers

Birds that are infected with avian influenza viruses can shed virus in saliva, nasal secretions, and feces. Activities that could result in exposure to avian influenza-infected poultry include euthanasia, carcass disposal, and cleaning and disinfection of premises affected by avian influenza. These activities are unlikely to occur in an urban area such as San Francisco. However, the CDC has written interim guidance for protection of persons involved in control of avian influenza outbreaks among poultry in the USA (www.cdc.gov/flu/avian/professional/protect-guid.htm).

Health Care Providers

Human influenza is transmitted primarily via large respiratory droplets, and isolation precautions for typical human influenza include Standard plus Droplet Precautions. However, the CDC has recommended additional precautions for healthcare workers involved in the care of patients with documented or suspected avian influenza, for the following reasons: 1) higher risk of serious disease and increased mortality from HPAI; 2) each human infection represents an important opportunity for avian influenza to further adapt to humans and gain the ability to transmit more easily among people; and 3) any opportunities for human-to-human transmission of avian influenza may increase opportunities for genetic reassortment and possible emergence of a pandemic strain.

* For description of Precautions, see Chapter on Infection Control

The most recent (May, 2004) CDC recommendations state:

- All patients who present to a health-care setting with fever and respiratory symptoms should be managed according to recommendations for respiratory hygiene and cough etiquette (www.cdc.gov/flu/professionals/infectioncontrol) and questioned regarding their recent travel history.
- Patients with a history of travel within 10 days to a country with avian influenza activity and who are hospitalized with a severe febrile respiratory illness, or are otherwise under evaluation for avian influenza, should be managed using **Standard plus Contact plus Airborne Precautions.** In addition, **Eye Protection** should be utilized when within 3 feet of the patient. These precautions should be continued for 14 days after onset of symptoms or until either an alternative diagnosis is established or diagnostic test results indicate that the patient is not infected with influenza A virus.
- Patients managed as outpatients or hospitalized patients discharged before 14 days with suspected avian influenza should be isolated in the home setting, following CDC guidelines for home isolation of SARS patients (www.cdc.gov/ncidod/sars/guidance/i/pdf/i.pdf).

CDC guidance also recommends that healthcare workers who may come into contact with the H5N1 virus or with infected patients should be vaccinated with the most recent seasonal influenza vaccine. Although this will not protect against H5N1 influenza A, it will help avoid simultaneous infection with other influenza strains and may thereby decrease the risk of genetic reassortment.

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BOTULISM

Outline

Immediately report any suspected or confirmed cases of botulism to:
SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830)

- By law, health care providers must report suspected or confirmed cases of botulism to their local health department immediately [within 1 hr].
- SFDPH Communicable Disease Control can facilitate specialized testing and will initiate the public health response as needed.

Also notify your:

- Infection Control Professional
- Clinical Laboratory

INTRODUCTION

Botulism is a disease caused by exposure to botulinum toxin produced from *Clostridium* species, mainly *Clostridium botulinum*. Clinical forms of the disease include foodborne, inhalational, wound, infant, adult intestinal toxemia, and iatrogenic. *C. botulinum* is a gram-positive, strictly anaerobic, spore-forming bacillus naturally found in soil and aquatic sediments. There are seven types of the toxin based on antigenic differences, labeled A through G. Types A, B, and E (and rarely, F) are pathogenic in humans. Types C, D, and E cause illness in other mammals, birds, and fish. Botulinum toxin lacks color, odor, and taste and is the most lethal toxin known. Death is caused by doses of less than 1 μg. Antibiotics have no activity against the toxin itself.[1-3]

In response to unfavorable environmental conditions (changes in pH, temperature, and water or nutrient availability), *C. botulinum* bacteria sporulate. *C. botulinum* spores are hardy, resistant to dessication, heat, ultraviolet (UV) light, and alcohols, and can survive boiling for up to 4 hours; however, they are readily killed by chlorine-based disinfectants. Once spores encounter more favorable conditions, such as are found in contact with human tissues, they germinate, thereby producing growing cells that are capable of reproducing and elaborating toxin. .[1-3]

The Working Group for Civilian Biodefense considers botulism to be a dangerous potential biological weapon because of the pathogen's "extreme potency and lethality; its ease of production, transport, and misuse; and the need for prolonged intensive care among affected persons." Use of botulism as a biological weapon is expected to produce severe medical and public health outcomes.[3-6]

EPIDEMIOLOGY

Botulinum Toxin as a Biological Weapon

State-sponsored military programs have researched and weaponized botulinum toxin dating back to the 1930s. Botulism has also been used as a weapon by a terrorist group. Unfortunately, botulism is ubiquitous in nature and therefore access to it cannot be easily controlled.[3, 4]

Likely modes of dissemination for toxin used as a weapon include:[3-6]

- **Contamination of food or beverages**. Possible food or beverage vehicles for botulism toxin are those that are not heated at 85°C (185°F) for 5 minutes before consumption or those that are contaminated after appropriate heating. Typical pasteurization does not remove all toxin.

- **Dispersion of aerosolized toxin.** Animal studies and rare cases of laboratory accidents have confirmed the pathogenicity of aerosolized toxin. One study estimates that aerosolizing 1 g of botulinum toxin could kill up to 1.5 million people; while another estimates that a point source exposure could kill 10% of the population 500 meters downwind. Technical factors make such dissemination difficult.

- **Contamination of a water supply.** This is a possibility, but not likely because of the quantity of toxin needed to effectively contaminate a water supply. Additionally, standard drinking water treatment inactivates the toxin quickly and, in fresh water, it is inactivated through natural mechanisms in 3 to 6 days.

An intentional release of botulinum toxin would have the following characteristics:[3, 4, 6]

- Clustering in time: multiple similarly presenting cases of rapidly progressing acute flaccid symmetric paralysis with prominent bulbar palsies, generally 12 to 36 hours after release
- Atypical host characteristics: cases of unusual botulinum toxin type (C, D, F, G, and possibly E) *or* cases without typical gastrointestinal symptoms of nausea, vomitting, and diarrhea
- Unusual geographic clustering: cases in geographic proximity during the week before symptom onset, but lack common food exposure (aerosol exposure) *or* toxin type outside of typical geographic range
- Absent risk factors: multiple outbreaks without an association with a common food source

Naturally Occurring Botulism

Reservoirs

The sporulated form of the bacterium is commonly found in soils and aquatic sediments. Cistern water, dust and foods, including honey, can become contaminated from contact with the soil. [1, 2, 7]

Mode of Transmission

Botulism is caused by exposure to botulinum toxin. Humans can become infected in a number of ways:

- Inhalation of toxin (inhalational)

- Consumption of toxin (foodborne)
- Consumption of *C. botulinum* spores (infant; adult intestinal toxemia)
- Contamination of a tissue with *C. botulinum* spores (wound)
- Contamination of a tissue with toxin (iatrogenic)

Worldwide occurrence

In the late 1700s, botulism emerged as a disease because of changes in sausage production in Europe. In fact, *botulus* means sausage. Soon thereafter in the early 1800s, botulism associated with consumption of fermented fish was recognized in Russia. Wound and infant botulism were discovered much later in the mid to late 1900s. In 1999-2000, more than 2500 cases of foodborne botulism were reported in Europe. The highest incidence is found in countries of the former Soviet Union and in Asia and is related to improper food handling. Type B is more common in Europe, whereas type E is more common in Scandinavia and Canada and is frequently linked to improper storage of fish and marine mammals.[1, 8]

United States Occurrence

In the United States, naturally occurring botulism is a rare disease with an annual incidence of approximately 100 cases (infant: 71; food: 24; and wound: 3).[9] More than half of foodborne cases occur in the Western states of California, Oregon, Washington, Alaska, and Colorado.[9] Type E is more common among Alaskan natives because of their diet of fermented meat from aquatic mammals and fish.[10] Type A is found mainly in Western states and type B is more common in the East.[1] Most cases of wound botulism result from injection drug use with black tar heroin, which is more common in the Western states.[11]

Occurrence in California and San Francisco

From 1994 to 2006, 44 cases of foodborne botulism were reported in California, and one of these occurred in San Francisco.[12-15]

CLINICAL FEATURES

Regardless of the route of intoxication the same clinical neurologic syndrome develops.[1-3, 16] Botulism is an afebrile descending symmetric paralytic illness. Disease generally begins with absorption of toxin by mucosal surfaces in the gastrointestinal system, the eye or nonintact skin. Cranial nerve dysfunction ensues followed by muscle weakness beginning with the proximal muscle groups. Severity of disease is variable, ranging from mild cranial nerve dysfunction to flaccid paralysis. Both the severity of disease and the rapidity of onset correlate with the amount of toxin absorbed into the circulation.[3, 6]

Botulinum toxin blocks acetylcholine release at the neuromuscular junction of skeletal muscle neurons and peripheral muscarinic cholinergic autonomic synapses. It binds irreversibly to presynaptic receptors to inhibit the release of acetylcholine and cause neuromuscular weakness and autonomic dysfunction. The effect lasts weeks to months, until the synapses and axonal branches regenerate. Death from botulism results acutely from airway obstruction or paralysis of respiratory muscles. .[1-3]

The case fatality rate was close to 60% prior to the advent of critical care. Even today, the mortality rate is high if treatment is not immediate and proper. In an outbreak setting, the mortality rate for the first case is 25 % and for all other cases is 4%. A shorter incubation period has been linked to higher mortality, possibly reflecting a dose-dependent response. Fatality doubles in persons above the age of 60.[1-3]

Food-borne botulism occurs from the consumption of preformed botulinum toxin in food. Waterborne botulism has not been seen. Toxin types A, B, and E account for most cases of foodborne botulism. Minute amounts of toxin can cause disease. A case in which a contaminated potato was spit out before being swallowed, resulted in 6 months of hospitalization.

In order for foodborne botulism to occur:[1, 8]

- *C. botulinum* spores must contaminate the food
- anaerobic, nonacidic, low sugar and salt, and warm conditions must be met during the food preservation so that the spores can survive, germinate and produce toxin
- the food must not be reheated sufficiently to inactivate the heat-labile toxin before the food is consumed ($\geq$85°C for 5 minutes).

Inhalational botulism does not occur in nature; however three human cases occurred in 1962 in lab technicians working with aerosolized botulinum toxin. It has also been produced experimentally in laboratory animals.

Wound botulism is caused by toxin absorbed into the circulation through a wound. Most cases are related to injection drug use, especially in association with use of black tar heroin being injected into soft tissue ("skin popping").[11]

Infant botulism occurs from the consumption of *C. botulinum* spores. The spores invade the gastrointestinal tract, replicate, and release toxin, which is absorbed into the circulation. The source of spores typically is unknown, although ingestion of corn syrup or raw honey accounts for some cases.

Adult intestinal toxemia (or undefined) botulism occurs from the consumption of *C. botulinum* spores. Characteristics include unknown source of toxin, presence of toxin in stool, and abnormal gastrointestinal pathology (e.g., Billroth surgery, Crohn's disease, and peptic ulcer disease) or antimicrobial drug use.

Iatrogenic botulism been noted very rarely after medical use or misuse of the botulinum toxin. Purified, highly diluted, injectable botulinum toxin is used to treat a range of spastic or autonomic muscular disorders. Toxin type A (Botox) is used in extremely minute doses for the treatment of facial wrinkles and blepharospasm, cervical dystonia strabismus, glabellar lines, and primary axillary hyperhidrosis. Toxin type B (Myobloc, Neurobloc) is used to treat cervical dystonia. Dysphagia, limited paresis and other neuromuscular impairment of the toxin are symtoms that have been seen.[17]

CLINICAL FEATURES: BOTULISM[1-3, 6, 16]	
Incubation Period	• 12-80 hours (range 2 hours to 8 days)
Transmission	• Inhalation of toxin • Consumption of toxin or *C. botulinum* spores • Contamination of a tissue with toxin or *C. botulinum* spores
Signs and Symptoms	Cardinal signs • Afebrile • Symmetrical neurological manifestations • Normal mental status, though may appear lethargic and have difficulty with communication • Normal to slow heart rate without the presence of hypotension • Normal sensory nerve function, other than vision Early presentation – cranial nerve abnormalities • Fatigue and vertigo • Double and blurred vision, intermittent ptosis and disconjugate gaze • Difficulty swallowing food Later presentation – descending paralysis • Difficulty moving eyes and mild pupillary dilation and nystagmus • Tongue weakness, decreased gag reflex, indistinct speech, dysphagia, dysphonia • Symmetrical, descending progressive muscular weakness, especially arms and legs • Unsteady gait • Extreme weakness, including postural neck muscles and occasional mouth breathing • Autonomic nerve dysfunction; may include urinary retention, orthostasis • Constipation Ingestional: • Dry mouth and dysarthria • Nausea and vomiting, except when exposure is purified toxin Inhalational: • Mucus in throat • Serous nasal discharge, salivation Infant: • Inability to suck and swallow • Constipation • Weakened voice • Floppy neck
Progression and Complications	• Respiratory failure and possible aspiration pneumonia • Residual fatigue, dry mouth or eyes, dyspnea on exertion several years later
Laboratory and Radiographic Findings	• Normal CSF values • Normal CBC • Normal imaging of brain and spine (CT scan or MRI) Characteristic EMG findings include: • Decremented response to repetitive nerve stimulation at low frequency (3 Hz) • Facilitated response to repetitive nerve stimulation at high frequencies (10-50 Hz) • Low compound muscle action pontential
CBC, complete blood count; CSF, cerebrospinal fluid, CT, computed tomographic; EMG, electromyogram; MRI, magnetic resonance imaging.	

DIFFERENTIAL DIAGNOSIS

Diagnosis of botulism during the initial stages requires a high index of suspicion because of the lack of readily available rapid confirmatory tests.

Important questions to ask include:

- recent history of eating
    - home-canned or home-prepared vegetable, fruit, including foil-wrapped baked potato
    - lightly preserved or fermented meat and fish products, including seafood products from Alaska, Canada or the Great Lakes
- other known individuals with similar symptoms
- recent history of injection drug use, particularly with black tar heroin or cocaine

Key features that distinguish botulism are the constellation of:

- afebrile illness
- normal mental status
- cranial nerves prominently involved
- descending paralysis
- symmetric bilateral impairment
- absence of paresthesias
- normal CSF studies
- characteristic EMG findings

Other conditions to consider are:

- Guillain-Barre syndrome (especially Miller-Fisher syndrome)
- myasthenia gravis
- stroke or CNS tumor
- CNS infections (particularly of brainstem)
- Lambert-Eaton syndrome
- tick paralysis
- sudden infant death syndrome
- hyperemesis gravidarum
- saxitoxin (paralytic shellfish poisoning)
- tetrodotoxin (puffer fish poisoning)
- laryngeal trauma
- diabetic neuropathy
- poliomyelitis/West Nile acute flaccid paralysis
- psychiatric illness (i.e., conversion paralysis)
- inflammatory myopathy
- streptococcal pharyngitis
- viral syndrome
- hypothyroidism
- overexertion
- diphtheria
- Wernicke's encephalopathy
- intoxication with CNS depressants (atropine, aminoglycoside, magnesium, ethanol, organophosphates, nerve gas, carbon monoxide)

LABORATORY DIAGNOSIS

Routine laboratory and radiographic findings for specific clinical presentations of botulism are listed in the clinical features table.

If you are testing or considering testing for botulism, you should:

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830).** SFDPH can authorize and facilitate testing, and will initiate the public health response as needed.
- **Inform your lab that botulism is under suspicion.**

Although laboratory confirmation should be initiated as soon as possible if testing facilities are available, the clinical presentation should guide clinical management and public health interventions. Laboratory confirmation is challenging, but can be achieved in most cases by detection of botulinum toxin in serum, respiratory secretions, and stool via mouse bioassay, in which mice are injected with the patient sample and observed for the development of characteristic symptoms. Serum specimens must be taken *before* antitoxin treatment to demonstrate the presence of botulinum toxin. The test requires 1-4 days to complete and is performed only at reference laboratories. Electromyography provides diagnostic information more rapidly. Repetitive nerve stimulation at 20 to 50 Hz differentiates between various etiologies of acute flaccid paralysis. Electromyography is not recommended for infants.[3, 6, 16]

Because the laboratory diagnosis of botulism may take several days to complete, health department officials can authorize the release of antitoxin prior to laboratory confirmation on the basis of clinical findings and may be able to provide other rapid detection tests that are currently investigational (e.g., time-resolved fluorescence assay, toxin micronanosensor, ganglioside-liposome immunoassay, enzyme-linked immunosorbent assay [ELISA]).

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfcdcp.org).

Treatment

Outcome is based on early diagnosis and treatment. Supportive care (including airway protection, mechanical ventilation, and feeding by central tube or parenteral nutrition) and timely administration of equine botulinum antitoxin are keys to the successful management of botulism.[2, 3, 18] Establish a means of communication early because sometimes conditions such as debilitating headaches are not communicated after the onset of paralysis.

Antitoxin

Antitoxin administration should not be delayed for laboratory confirmation because antitoxin does not reverse disease or existing paralysis, but only stops progression of disease.

Patients given antitoxin within the first 24 hours after symptom onset had shorter hospital stays, shorter duration of ventilatory support, and a lower fatality rate (10%) than those given antitoxin more than 24 hours after onset (15%) or those who did not receive antitoxin at all (46%).[19, 20]

Antitoxin is provided by the Centers for Disease Control and Prevention (CDC) but is available for release only by the state or local health departments. Delivery can be expected within 12 hours of request.

Consult public health authorities regarding dosage, because recommendations change. Currently, the CDC recommends immediate intravenous administration of the trivalent antitoxin (one vial diluted 1:10 over 30 minutes). If it is suspected that the exposure was to an extremely high dosage of toxin, the serum may be tested after treatment for the presence of remaining toxin.[16]

Because antitoxin is of equine origin, hypersensitivity reactions can occur. From 1967 to 1977, 9% of persons treated with botulinal antitoxin had a nonfatal hypersensitivity reaction.[21] In recent years, when the recommended dosage has decreased 2- to 4-fold, less than 1% have experienced hypersensitivity reactions.[2] A skin test may be valuable in patients with allergies, previous anaphylaxis, or prior receipt of equine antitoxins. If skin testing is positive, consider desensitizing over several hours before administering the complete dose of antitoxin or pretreat with antihistamines, steroids, and epinephrine infusions. Diphenhydramine, epinephrine, and airway equipment should be easily accessible during any administration.

Human botulism immune globulin is used to treat infants, which is administered intravenously.[22]

Supportive care

Ventilatory support may be required for several weeks or more. One study found the mean time on a ventilator for botulism cases was 58 days.[20]

With modern intensive care methods, case fatality rates for botulism in the United States have dropped to less than 10%. In a mass casualty setting, measurement and management of ventilatory function may pose challenges because of limited ventilator capacities. Local health departments can request supplemental laryngoscopes, endotracheal tubes, and Ambu bags from the CDC. If personnel are limited, consider recruiting health civilians for bag ventilation.

A reverse Trendelenburg positioning with cervical vertebral support has been beneficial in terms of respiratory mechanics and airway protection in nonventilated infants with botulism, but has not been tested in adults. In adults, especially those with obesity, a 20- to 25-degree angle may be beneficial.[3]

Utilize physical therapy and physical turning to minimize intensive care complications.

Secondary infections

Antibiotics may be used for treatment of secondary infections; however, aminoglycosides and clindamycin are contraindicated because they may exacerbate the neuromuscular blockade.[3]

Post-exposure prophylaxis

There is currently no available postexposure prophylaxis for asymptomatic exposed persons.[3, 16] Such persons should be educated regarding the signs and symptoms of clinical botulism and instructed to seek medical care immediately if symptoms occur. Not all exposed persons will develop clinical symptoms. Exposed persons and their families may experience anxiety and/or somatic symptoms that may include neurologic symptoms. These patients should be carefully assessed. Antitoxin supplies are limited, and therapy will be reserved for patients with compatible neurological findings.

Vaccine

Preexposure immunization with botulinum toxoid is restricted to certain laboratory and military personnel. Supplies are extremely limited and would not be available for the public.[3, 16]

COMPLICATIONS AND ADMISSION CRITERIA

In patients with botulism, cranial nerve dysfunction progresses inexorably to a symmetric, descending muscle weakness or paralysis. Respiratory failure occurs in 40-70% of botulism patients because of declining upper airway and ventilatory muscle strength. Additional complications of botulism include secondary infection of the respiratory system and sequelae related to intubation and mechanical ventilation, prolonged immobilization, and autonomic dysfunction. Diminished respiratory muscle function and easy fatigability were described by botulism patients 2 years after recovery.

Hospital admission is required for protection of the airway, mechanical ventilatory support, and fluid and nutritional management until normal muscular function returns.

INFECTION CONTROL

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfcdcp.org).

Clinicians should notify local public health authorities and their laboratory of any suspected botulism case. Health authorities may conduct epidemiologic investigations and implement disease control interventions to protect the public. Both HICPAC (Hospital Infection Control Practices Advisory Committee) of the CDC and the Working Group for Civilian Biodefense recommend **Standard Precautions** for botulism patients in a hospital setting without the need for isolation. Person-to-person transmission does not occur.[3, 16, 23]

Decontamination

After exposure to toxin, wash clothes and skin with soap and water. Inactivation of the toxin in the environment can take 2 days; however, changes in temperature and humidity can affect the rate of decomposition. Contaminated surfaces and spills of cultures or toxin can be disinfected with

sodium hypochlorite (0.1% which is a 1:50 dilution of household bleach) or sodium hydroxide (0.1N). Moist heat at 120°C for at least 15 minutes destroys spores.[3]

PEARLS AND PITFALLS

1. Botulism is often misdiagnosed as a polyradiculopathy (Guillain-Barre syndrome or Miller-Fisher syndrome), myasthenia gravis, or other diseases of the central nervous system. Botulism is distinguished from other flaccid paralyses by its initial presentation with prominent cranial neuropathy, its subsequent descending, symmetrical paralysis, and its absence of sensory nerve deficits.

2. In the United States, botulism is more likely than Guillain-Barre syndrome, chemical poisoning, or poliomyelitis to cause a cluster of cases of acute flaccid paralysis.

3. Botulism antitoxin neutralizes freely circulating toxin but does not dislodge toxin already bound to presynaptic receptors. Early administration of antitoxin can help to inhibit further paralysis, but does not reverse paralysis that has already occurred.

4. Botulism antitoxin is limited in quantity and is available only through public health authorities. Since the laboratory diagnosis of botulism requires an in-vivo assay and may take several days to complete, health department officials often authorize the release of antitoxin prior to laboratory confirmation, on the basis of clinical findings.

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BRUCELLOSIS

AUGUST 2005

Outline

By law, health care providers must report suspected or confirmed Brucellosis to the local health department immediately (within 1 hr).

Even a single case of Brucellosis is considered an outbreak and is a public health emergency.

To report: call SFDPH communicable disease control (24/7 Tel: 415-554-2830).

Upon receipt, SFDPH will initiate the public health response and can facilitate lab testing.

AGENT

Brucellosis is a zoonotic disease of domestic and wild animals, caused by the non-motile, non-sporulating, small, gram-negative coccobacilli bacteria of the genus *Brucella.* Four species can be pathogenic in humans: *B. melitensis, B. abortus, B. canis* and *B. suis*. They are highly infectious, especially *B. melitensis* and *B. suis*.

Brucellae contain lipopolysaccharide (LPS) in the outer cell membrane, however this LPS is structurally different from that of the Enterobacteriaceae, and this feature may underlie the reduced pyrogenicity (less than 1/100th) of *Brucella* LPS compared with *E. coli* LPS.

EPIDEMIOLOGY

Brucellosis as a Biological Weapon

The US military developed *B. suis* as a biological weapon in the 1950's, but terminated this program in 1967. Their transmissibility by aerosol suggests that *Brucella* organisms might be a candidate for use as a bioweapon. Fewer than 100 organisms could constitute an infectious aerosol. The CDC considers brucellosis a lesser threat than agents such as anthrax and smallpox: its incubation period is rather long, many infections are asymptomatic, and the mortality is low. However, it might be used as an incapacitating agent as it often causes a protracted illness.

The most likely form of intentional release would be via infectious aerosols; however food-borne exposure is also possible. Any large-scale outbreak of brucellosis would suggest deliberate release of *Brucella* organisms. Bioterrorism might also be suggested by clusters of brucellosis cases without a travel history to endemic areas, without relevant foodborne or occupational exposures, or where the cases are linked in time and place (e.g. geographically related cases following a wind direction pattern).

Naturally Occurring Brucellosis

Brucella species infect mainly ruminant mammals, including cattle, sheep, goats, pigs, and camels, in which they cause genital infection, abortion, and fetal death. Additional animal reservoirs include elk, caribou, bison, deer, and wild and domestic canines. Animals may transmit *Brucella* organisms during septic abortion, at the time of slaughter, and in their milk. Humans are usually infected incidentally in one of three ways:

- Direct contact with the tissues of infected animals. Occupational exposures include those of veterinarians, shepherds, ranchers, and slaughterhouse workers, who are believed to become infected through skin abrasions, cuts, or conjunctival exposure.

- Ingestion of contaminated food or water. Consumption of contaminated milk products is the most common mode of acquisition worldwide. Pasteurization of dairy products prevents transmission and has drastically reduced the incidence of brucellosis in the developed world. Meat products are rarely the source of infection because they are not usually eaten raw and the number of organisms in muscle tissue is low.

- Inhalation of infectious aerosols. The inhalational route is of consequence for occupational exposures listed above, particularly slaughterhouse workers, and may also constitute a risk factor for laboratory workers who culture *Brucella* bacteria.

Naturally occurring exposures to brucellosis are unusual in the USA and tend to be isolated. Fewer than 200 total cases per year are reported in the United States, most of these in Texas and California. During the period 1994-2003 there were 275 total cases reported in California; of these, 2 occurred in San Francisco. The epidemiology of brucellosis in Texas and California has changed from a disease associated with exposure to cattle to one linked to the ingestion of unpasteurized goat milk products ("queso fresco") imported from Mexico.

Disease incidence is much higher in the Middle East and Mediterranean regions, and in China, India, and Latin America.

CLINICAL FEATURES

The brucellae are facultative intracellular pathogens that can survive and multiply within the phagocytic cells of the host. After entering the human body and being taken up by local tissue lymphocytes, brucellae are transferred through regional lymph nodes into the circulation and are subsequently seeded throughout the body, with tropism for the reticuloendothelial system.

Clinical manifestations of brucellosis are diverse and often non-specific, and the course of the disease is variable. For most exposures, the clinical syndrome does not clearly relate to the portal of entry of the organism; however those exposed via the aerosol route may have increased frequency of respiratory symptoms. *B. melitensis* tends to cause more severe, systemic illness than the other brucellae; *B. suis* is more likely to cause localized, suppurative disease.

BRUCELLOSIS: CLINICAL FEATURES	
Incubation Period	2-4 weeks (range 5 days to several months)
Signs & Symptoms	• Fever always occurs; spiking or "undulant" pattern may be apparent • May have acute, subacute, or chronic presentation • Other consitutional symptoms: malaise, anorexia, back pain, myalgias, arthralgias, headache • "Malodorous perspiration" • Mild lymphadenopathy (10-20%) • Hepatomegaly or splenomegaly (20-30%) • Nonspecific skin lesions (papules, ulcers, e. nodosum, petechiae) in 5% • Weight loss among chronically infected • Almost any organ system can be involved • Most affected persons recover in 3-12 months, however a minority may develop one or more of the complications below
Complications	• Skeletal: osteomyelitis (most common); also sacroiliitis, spondylitis, peripheral arthritis • Reproductive: spontaneous abortion; epididymo-orchitis • GI: acute ileitis, hepatitis, liver abscess, liver granuloma • CNS: meningitis, encephalitis, brain abscess, myelitis • CV: endocarditis, pericarditis • Pulmonary: bronchitis, pneumonia, lung nodules, abscess, hilar adenopathy, pleural effusion/empyema, lung abscess • Uveitis
Laboratory Findings	• Mild leukopenia with relative lymphocytosis • Mild anemia and thrombocytopenia may be present; DIC is rare • Other abnormalities are related to the organ system involved

DIFFERENTIAL DIAGNOSIS

Due to the non-specific presentation and numerous, varied complications of brucellosis in humans, the differential diagnosis is vast and will not be addressed in detail here. A high index of suspicion is necessary to diagnose brucellosis, due both to the non-specific presentation and to the relatively long latency period between inoculation and the development of symptoms.

Key clinical questions that help to suggest naturally-acquired brucella infection include:

- History of contact with ruminant mammals, via occupational or recreational exposures (veterinarians, slaughterhouse workers, ranchers, shepherds, laboratory workers, visitors to dairy farms or petting zoos)
- Consumption of unpasteurized milk products (e.g. "queso fresco")
- Travel to areas where brucellae are established in the animal population

In the setting of intentional attack using brucella, these exposures may be notably absent.

LABORATORY DIAGNOSIS

Definitive diagnosis of brucellosis is made when brucellae are recovered from infected tissues, typically blood or bone marrow. The rate of isolation ranges from 15-70%. The organism has also been recovered from urine, CSF, synovial fluid, and biopsies of liver and lymph nodes. *Brucella* species often require several weeks to grow in culture, so this method is not useful for rapid identification.

If you are testing or considering testing for Brucellosis, you should:

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830)**
- **Notify the lab that Brucellosis is suspected, as the organism may pose a risk to personnel.**

Neither CDC nor the Working Group on Civilian Biodefense has issued bioterrorism-specific treatment/prophylaxis recommendations for Brucellosis. SFDPH will provide situational guidance in response to events (www.sfdph.org/cdcp).

A presumptive diagnosis can be made using specific antibody titers. The serum agglutination test (SAT) is based on antibody against lipopolysaccharide. Most cases of active infection have a single titer of 1:160 or higher. Drawbacks of the SAT include the inability to diagnose *B. canis* infection, cross-reaction with other gram-negative organisms, and the lack of seroconversion in some cases. Also, SAT are not suitable for patient follow-up since titers can remain elevated for a prolonged period. The ELISA test for brucellosis relies on cytoplasmic antigens and is both more sensitive and more specific than SAT. However, like SAT, titers can remain elevated for prolonged periods. A number of variations of PCR tests are becoming available, but standardization is still lacking.

TREATMENT AND PROPHYLAXIS

Treatment

Generally accepted principles of brucellosis treatment are that the antibiotics used must penetrate macrophages, and that monotherapy has a higher rate of relapse compared with combined therapy regimens.

BICHAT, the European Commission's Task Force on Biological and Chemical Agent Threats, has recommended as first-line therapy: Doxycline 100 mg IV/PO twice daily, combined with **either** streptomycin 1 gm IM once or twice daily for up to 2 weeks; **OR** rifampin 600-900 mg PO daily for 6 weeks; **OR** gentamicin 5 mg/kg/day IV in 2 divided doses for up to 2 weeks. This regimen, dosage-adjusted to body weight, is also first-line treatment for children >8 years old. Treatment with trimethoprim-sulfamethoxazole (TMP-SMX) plus rifampin is recommended for pregnant women and for children <8 years of age. Quinolones have been used with success against Brucellae, while macrolide antibiotics are not effective. Complications of brucellosis are also ed with 2-drug regimens, while neurobrucellosis has generally been treated with 3 agents.

Relapses occur in about 10% of cases, usually during the first year after infection, and are often milder in severity than the initial disease. Relapse has been managed with a repeated course of the usual antibiotic regimens. Most cases of relapse are felt to be caused by inadequate treatment.

Post-Exposure Prophylaxis

There is little evidence to support the utility of post-exposure prophylaxis against brucellosis in humans. BICHAT has recommended a 3-6 week course of doxycycline **OR** TMP-SMX, with the addition of rifampin to either drug. **In the event of outbreak, SFDPH will provide updated, situational guidelines for prophylaxis (www.sfdph.org/cdcp).**

Vaccination

There is currently no licensed vaccine available for brucellosis. Some limited clinical data exist on a live, attenuated vaccine candidate, but licensing and production of this vaccine are not anticipated.

INFECTION CONTROL*

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfdph.org/cdcp).

Person-to-person transmission of brucellosis is extremely rare. **Standard Precautions** are considered adequate for patients with brucellosis.

Brucella is sensitive to exposure to heat and most disinfectants but can survive in the environment for up to two years under specific conditions, becoming a continuing threat to both humans and animals.

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PLAGUE

JUNE 2008

Outline

Immediately report any suspected or confirmed cases of plague to:

SFDPH Communicable Disease Control
(24/7 Tel: 415-554-2830)

- By law, health care providers must report suspected or confirmed cases of plague to their local health department immediately [within 1 hr].
- SFDPH Communicable Disease Control can facilitate specialized testing and will initiate the public health response as needed.

Also notify your:

- Infection Control Professional
- Clinical Laboratory

INTRODUCTION

Plague is an acute bacterial infection caused by *Yersinia pestis*, a member of the family *Enterobacteriaceae*. *Y. pestis* is a pleomorphic, nonmotile, nonsporulating, intracellular, Gram-negative bacillus that has a characteristic bipolar appearance on Wright, Giemsa, and Wayson's stains. There are three virulent biovars: *antiqua, medievalis,* and *orientalis* and a fourth avirulent biovar, *microtu*.[1, 2] The *orientalis* biovar is thought to have originated in southern China and caused the most recent pandemic.[3]

The Working Group for Civilian Biodefense considers plague to be a potential biological weapon because of the pathogen's availability "around the world, capacity for its mass production and aerosol dissemination, difficulty in preventing such activities, high fatality rate of pneumonic plague, and potential for secondary spread of cases during an epidemic." Of the potential ways that *Y. pestis* could be used as a biological weapon, aerosol release would be most likely. This method has been successfully demonstrated to cause disease in Rhesus macaques.[4]

EPIDEMIOLOGY

Plague as a Biological Weapon

In the 20th century, countries including the United States, the former Soviet Union, and Japan developed ways for using *Y. pestis* as a weapon.[5-7] Creating aerosolized plague is technically challenging; however, if an intentional release of aerosolized plague were to take place, an outbreak of pneumonic plague would be likely. This would be of serious concern because of the high case-fatality rate and the potential for person-to-person transmission.[4, 7, 8]

An outbreak of disease caused by an intentional release of *Y. pestis* would have the following characteristics:

- Clustering in time: multiple similarly presenting cases of severe, progressive multilobar pneumonia, generally 2-4 days after release (range of 1 to 6 days)
- Atypical host characteristics: unexpected, unexplained cases of acute illness in previously healthy persons who rapidly develop severe, progressive multilobar pneumonia with hemoptysis and gastrointestinal symptoms
- Unusual geographic clustering: multiple cases in an urban area where naturally occurring plague is not endemic
- Absence of risk factors: patients lack plague exposure risk factors (e.g., recent flea bite; exposure to rodents, especially rabbits, squirrels, wood rat, chipmunk, or prairie dogs; scratches or bites from infected domestic cats)

Intentionally-released *Y. pestis* strains may be altered to have enhanced virulence, antimicrobial resistance, or increased ability to evade vaccines and diagnostic tests.[4, 7]

Naturally Occurring Plague

Reservoirs

The natural reservoir for *Y. pestis* is primarily wild rodents. Around the world, the domestic rat has been associated with the most human cases; however in the western United States, burrowing rodents (e.g., ground squirrels, rock squirrels, and prairie dogs) are the most important reservoir.[9] A recent study has found soil to be a potential reservoir, with Y. pestis persisting from months to several years n association with wild rodents.[10, 11] Other mammals that act as hosts include cats, goats, sheep, camels, and humans.[10, 12-17] Human plague cases often follow epizootics in local rodent populations.[10, 18, 19]

Mode of Transmission

Humans can become infected in a number of ways:[4, 13, 14, 16, 17, 20]

- Bite of infected rat flea
- Direct contact with infected draining buboes
- Direct contact (including bites or scratches) with infected animals
- Inhalation of respiratory droplets from pneumonic plague-infected humans or animals (within 2 meters)
- Ingestion of bacteria (e.g., eating infected meat)

Human plague cases in nature are most commonly acquired from animal reservoirs via bites of the Oriental rat flea.[9, 21]

Worldwide occurrence

The first recorded plague pandemic was the Justinian plague (541-767 AD) which caused ~100 million deaths and is thought to have contributed to the demise of the Roman Empire. The second pandemic, also known as the Black Death, lasted from the 14th to the 19th centuries and was estimated to have killed between a third and a half of Europe's population. The third and most recent pandemic began in 1894 in China and caused an estimated 12 million deaths.[14, 19, 22, 23] Recent outbreaks in humans have included India (1994), Zambia (1996), Indonesia (1997), Algeria

(2003), Uganda (2004), and the Congo (2005).[24-28] Approximately 1,800 worldwide cases of plague are reported annually to the WHO, from all continents except Europe and Australia.[10]

Occurrence in the United States

Ships carrying infected rats introduced plague to the Americas via the ports on the Pacific Ocean and Gulf of Mexico in the early 1900s. In San Francisco, urban rats passed along the disease to native rodent populations. Eventually, plague spread across the western half of the United States and has been found in the native rodent population, their fleas, and their predators. Naturally occurring human plague generally occurs during the summer months in persons exposed to the reservoir.[27, 29] The last urban plague outbreak in the US occurred in Los Angeles in 1925.[25-27, 30]

From 1990 to 2005, a median of 7 cases of plague per year were reported in the US.[26] Based on provisional data, in 2006, there were 17 cases, and in 2007, 7 cases.[31]

Occurrence in California and San Francisco

From 1994 to 2007, 9 cases of plague were reported in California, and none of these occurred in San Francisco.[32-35]

CLINICAL FEATURES

Human plague occurs in many forms, determined primarily by the route of infection. The most common forms of plague in humans are bubonic plague, septicemic plague, and pneumonic plague. These are presented in detail below.

Plague infection is a severe clinical illness that can be life-threatening. Case fatality rates vary based on the route of infection. Mortality was historically much higher with nearly 100% mortality for untreated septicemic and pneumonic plague and 50-60% mortality for untreated bubonic plague cases. Administration of appropriate antibiotic treatment within the first 18 to 24 hours has decreased mortality rates to 30-50% for septicemic plague, 5-15% for pneumonic plague, and less than 5% for bubonic plague.[4] Thus, early administration of appropriate antibiotic treatment is critical, as poor outcomes occur with delays in seeking care and/or instituting effective antimicrobial treatment.

Pneumonic Plague

Primary pneumonic plague occurs when the organism is inhaled in respiratory droplets from infected humans or animals or in infectious aerosols accidentally or intentionally produced (e.g., spilled lab specimen or bioterrorism related release). Secondary pneumonic plague occurs when there is hematogenous spread of the organism to the lung. Primary pneumonic plague causes a more acute and fulminant disease. Pneumonic plague is not highly contagious but transmission can occur with prolonged close contact (within 2 meters) with a coughing patient in the end stage of illness. In a recent outbreak in Uganda, 1.3 pneumonic plague transmissions per pneumonic plague case were reported.[24] If untreated, pneumonic plague can spread and progress to septicemic plague.

PNEUMONIC PLAGUE	
Incubation period	• 1-4 days, with a maximum of 6 days
Transmission	• Inhalation of contaminated aerosol • Inhalation of respiratory droplets from pneumonic plague-infected humans or animals (within 2 meters) • Secondary hematogenous spread to the lung
Signs and symptoms	• Acute fever, chills, malaise, myalgia, headache • Productive cough, with sputum becoming more and more bloody • Chest pain, dyspnea, cyanosis • Tachypnea in children • Gastrointestinal symptoms
Progression and complications	• Refractory pulmonary syndrome • Adult respiratory distress syndrome • Septicemia
Laboratory and Radiographic Findings	• Leukocytosis with left shift • Gram-negative bipolar bacilli on sputum smear • Elevated creatinine and abnormally high liver enzymes • CXR findings include alveolar infiltrates progressing to lobar consolidation, pleural effusion • Rarely, mediastinal widening on CXR due to adenopathy

Bubonic Plague

Yersinia pestis can cause bubonic plague in humans via the bite of an infected rodent flea. *Y. pestis* survives in the flea midgut after a blood meal from an infected host. The organism is transmitted to a new host when the flea regurgitates during its next feeding. *Y. pestis* migrates to regional lymph nodes where it causes hemorrhagic lymphadenitis, creating the swollen, painful buboes that are characteristic of bubonic plague. The organisms often enter the bloodstream, causing hemorrhagic lesions in distant lymph nodes and organs. If untreated, bubonic plague can spread and progress to pneumonic or septicemic plague. Approximately, 80% of cases develop bacteremia, 25% develop clinical septicemia and 10% develop pneumonia as a complication.

BUBONIC PLAGUE	
Incubation period	1-8 days
Transmission	• Bite of infected rat flea • Direct contact with infected draining buboes • Direct contact (including bites or scratches) with infected animals
Signs and symptoms	Major • Sudden onset of chills, high fever, headache, lethargy • Buboes - Swollen, red, painful lymph nodes in areas proximal to the inoculation site (e.g., inguinal, axillary or cervical areas) • Rapid pulse • Hypotension Other • Gastrointestinal discomfort • Restlessness, confusion, lack of coordination • Skin lesion at the site of the flea bite occurs in < 10% of cases • Buboes may rupture and suppurate in second week

Progression and complications	• Septicemia • Secondary pneumonic plague • Meningitis (rare)
Laboratory findings	• Leukocytosis with left shift • Gram-negative bipolar bacilli on bubo aspirate smear • Elevated creatinine and abnormally high liver enzymes

Septicemic Plague

In primary septicemic plague there is systemic sepsis caused by *Y. pestis,* but without noticeable, preceding lymph node or pulmonary involvement. Up to 25% of naturally-occurring plague cases may present with primary septicemic plague.[19] Secondary septicemic plague occurs commonly with either bubonic or pneumonic plague.

Septicemic plague causes a Gram-negative sepsis syndrome with multi-organ involvement, disseminated intravascular coagulation (DIC), and shock. In the late stages of infection, high-grade bacteremia often occurs, with identifiable organisms on peripheral blood smear.[18] Meningitis can occur and is characterized by cerebrospinal fluid (CSF) with many polymorphonuclear leukocytes.[9]

SEPTICEMIC PLAGUE	
Incubation period	1-4 days
Transmission	Site of primary infection may be unknown
Signs and symptoms	• Acute fever, chills, weakness, malaise • Gastrointestinal symptoms • Purpuric skin lesions and gangrene of the distal digits
Progression and complications	• Disseminated intravascular coagulation (DIC) • Shock • Multi-organ failure
Laboratory findings	• Leukocytosis with left shift and toxic granulation • Gram-negative bipolar bacilli on blood smear • Disseminated intravascular coagulation (DIC) • Elevated creatinine and abnormally high liver enzymes

Other syndromes caused by *Y. pestis* infection include:

- **Plague meningitis.** Although it is generally a complication of other forms of plague, it can be the presenting clinical syndrome. Plague meningitis results from hematogenous spread of *Y. pestis* organisms and is characterized by CSF with many polymorphonuclear leukocytes.[9]
- **Plague pharyngitis.** Plague pharyngitis generally results from direct inoculation of the pharynx. Eating raw infected meat is a risk factor. Clinically, plague pharyngitis presents as a severe pharyngitis or tonsillitis with cervical adenitis.
- **Pestis minor.** Pestis minor is a milder form of bubonic plague. Lymph nodes drain and patients convalesce without treatment.[10]

DIFFERENTIAL DIAGNOSIS

The diagnosis of plague during the initial stages requires a high index of suspicion because of the nonspecific, flu-like picture early in the disease. Early diagnosis is critical because prompt administration of antibiotics can decrease mortality.

Differential: Pneumonic Plague

Consider pneumonic plague in any case of severe Gram-negative pneumonia.

Key features that may help to distinguish plague pneumonia are:

Primary pneumonic plague:

- Rapid onset and rapid progression

Secondary pneumonic plague:

- Presence of painful adenitis (buboes)

Primary or secondary pneumonic plague:

- No response to typical antibiotic therapy for community-acquired pneumonia
- Hemoptysis in late stages of disease

Other conditions to consider are:

- bacterial pneumonia (*Mycoplasma, Legionella, Staphylococcus, Streptococcus, Haemophilus, Klebsiella, Moraxella*)
- viral pneumonia (influenza, respiratory syncytial virus [RSV], cytomegalovirus [CMV], hantavirus, severe acute respiratory syndrome [SARS])
- *Chlamydia* infection
- Q fever
- inhalation anthrax
- tularemia
- ricin
- rickettsial infections
- aerosolized exposure to staphylococcal enterotoxin B

Differential: Bubonic Plague

A key feature that may help to distinguish bubonic plague is:

- Presence of painful adenitis (buboes) progressing to systemic disease

Other conditions to consider are:

- cat scratch disease (*Bartonella*)
- ulceroglandular tularemia
- adenitis due to staphylococcal, streptococcal, or filarial infection
- tuberculosis
- non-tuberculosis mycobacterial infection
- lymphogranuloma venereum
- *Capnocytophaga canimorsus* infection
- chancroid
- primary genital herpes
- primary or secondary syphilis
- appendicitis
- strangulated inguinal or femoral hernia
- lymphadenopathy (secondary lymphoma, Kikuchi's lymphadenitis, systemic lupus erythematosus, toxoplasmosis, infectious mononucleosis)

Differential: Septicemic Plague

Key features that may help to distinguish septicemic plague are:

Primary septicemic plague:

- Absence of painful adenitis (buboes) or pulmonary involvement

Secondary septicemic plague:

- Presence of painful adenitis (buboes)

Other conditions to consider are:

- Gram-negative sepsis
- Gram-positive sepsis (*Staphylococcus*)
- meningococcemia
- rickettsial infections
- malaria
- louse-borne relapsing fever
- appendicitis

LABORATORY DIAGNOSIS

Routine laboratory and radiographic findings for specific clinical presentations of plague are listed in the clinical features tables.

If you are testing or considering testing for plague, you should:

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830).** SFDPH can authorize and facilitate testing, and will initiate the public health response as needed.
- **Inform your lab that plague is under suspicion. Some commercial bacterial test systems cannot reliably identify *Y. pestis.***

Initial identification of the organism relies on microscopic evaluation of infected tissue (blood, sputum, CSF, or fluid aspirated from a bubo or skin lesion scraping). Staining of the infected tissue may reveal Gram-negative bacilli (Gram stain) and bipolar staining (Wright, Giemsa, or Wayson stain).[4, 9] Order a Gram stain, culture, and Giemsa, Wright or Wayson stain of the material. Store and transport blood at room temperature. Transport other samples at room temperature, but store under refrigeration if transport time will be > 2 hours.

Although recommended, culture and isolation may be difficult. Blood and site-specific specimens should be collected prior to antibiotic administration as sterilization can occur rapidly. *Y. pestis* is slow-growing in culture and may not demonstrate growth until 48 hours after inoculation. Also, many commercial bacterial identification systems may misidentify *Y. pestis*.[4] To improve yield and ensure biosafety precautions, clinicians should notify laboratory personnel when plague is suspected.

Although rapid diagnostic tests are not widely available, the public health laboratory system may have access to rapid diagnostic testing on clinical specimens (e.g., polymerase chain reaction [PCR] or direct fluorescent antibody testing for *Y. pestis* F1 antigen).

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfcdcp.org).

Treatment

Supportive care and timely administration of antibiotics are the keys to successful management of plague. Plague pneumonia is often fatal if antibiotics are not begun within 12-24 hours of symptoms. Many patients will require intensive care with respiratory support because of complications of Gram-negative sepsis.

Resistant strains may occur either naturally or be engineered. In 1995, 2 distinct strains of naturally-occurring antibiotic-resistant *Y. pestis* were isolated from human cases of bubonic plague in Madagascar. One strain was resistant to all drugs recommended for plague treatment and prophylaxis and the other had high-level resistance to streptomycin. Both patients recovered with oral trimethoprim-sulfamethoxazole and intramuscular injections of streptomycin.[36, 37] In addition, *in vitro* resistance to imipenem and rifampin has been seen.[10]

Contained casualty setting: The Working Group recommends parenteral antimicrobial therapy when individual medical management is available. Antibiotics should be administered to all patients for 10 days. Therapy may be switched to oral antimicrobials when clinically indicated.

Mass casualty setting: Replacement of parenteral antibiotics with oral antibiotics may be indicated if the number of patients exceeds the medical care system's capacity to administer parenteral antibiotics.

PLAGUE - TREATMENT AND POST-EXPOSURE PROPHYLAXIS RECOMMENDATIONS[A]				
		Contained Casualty Setting	**Mass Casualty Setting**	**Post-Exposure Prophylaxis**
Duration of Rx		**10 days**	**10 days**	**7 days**
Adult	**Preferred**	**Streptomycin**, 1 gm IM q12 hrs ***or*** **Gentamicin**,[B] 5 mg/kg IM or IV q24 hrs, or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV q8 hrs	**Doxycycline**, 100 mg orally twice daily ***or*** **Ciprofloxacin**, 500 mg orally twice daily	
	Alternative [H]	**Doxycycline**[5,6], 100 mg IV q12 hrs or 200 mg IV q24 hrs ***or*** **Ciprofloxacin**, 400 mg IV q12 hrs ***or*** **Chloramphenicol**[C], 25 mg/kg IV q6 hrs (max 4 g/day)	**Chloramphenicol**[C], 25 mg/kg orally 4 times daily (max 4 g/day)	
Children	**Preferred**	**Streptomycin**, 15 mg/kg IM q12 hrs (max 2 g/day) ***or*** **Gentamicin**[B], 2.5 mg/kg IM or IV q8 hrs	**Doxycycline**[E,F]: ≥45 kg, give adult dosage <45 kg, give 2.2 mg/kg orally twice daily (max 200 mg/day) ***or*** **Ciprofloxacin**[E,G], 20 mg/kg orally twice daily (max 1 g/day)	
	Alternative [H]	**Doxycycline**[E,F]: ≥45 kg, give adult dosage <45 kg, give 2.2 mg/kg IV q12 hrs (max 200 mg/day) ***or*** **Ciprofloxacin**[E,G], 15 mg/kg IV q12 hrs (max 1 g/day) ***or*** **Chloramphenicol**[C,D], 25 mg/kg IV q6 hrs (max 4 g/day)	**Chloramphenicol**[C,D], 25 mg/kg orally 4 times daily (max 4 g/day)	
Pregnant Women	**Preferred**	**Gentamicin**[B], 5 mg/kg IM or IV q24 hrs or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV q8 hrs	**Doxycycline**[E,F], 100 mg orally twice daily ***or*** **Ciprofloxacin**[E], 500 mg orally twice daily	
	Alternative [H]	**Doxycycline**[E,F], 100 mg IV q12 hrs or 200 mg IV q24 hrs ***or*** **Ciprofloxacin**[E], 400 mg IV q12 hrs	**Chloramphenicol**[C,D], 25 mg/kg orally 4 times daily	

For plague meningitis, pleuritis, or myocarditis: Chloramphenicol should be used for 21 days for conditions when tissue penetration is important[4]. Irreversible marrow aplasia is rare (1 in 40,000 patients).

[A] Treatment recommendations come from the Working Group of Civilian Biodefense and may not necessarily be approved by the US Food and Drug Administration. Table adapted from JAMA. 2000;283:2281-2290.

[B] Aminoglycoside doses must be further adjusted for newborns, and according to renal function.

[C] Therapeutic concentration is 5 - 20 mcg/mL; concentrations >25 mcg/mL can cause reversible bone marrow suppression.

[D] According to the Working Group on Civilian Biodefense, children younger than 2 years of age should not receive chloramphenicol due to risk of 'gray baby syndrome'; however, the American Academy of Pediatrics has recommended chloramphenicol as the drug of choice for plague meningitis in children.

[E] Tetracycline and quinolone antibiotics are generally not recommended during pregnancy or childhood; however their use may be indicated for life-threatening illness.

[F] Ciprofloxacin may be preferred in pregnant women and children up to 8 years of age because of the known adverse event profile of doxycycline (e.g., tooth discoloration).

[G] Doxycycline may be preferred in children 8 years and older because of the adverse event profile of ciprofloxacin (e.g., arthropathies).

[H] Trimethoprim-sulfamethoxazole has been successfully used to treat plague; however the Working Group considers this a second tier choice.

Post-Exposure Prophylaxis

Post-exposure prophylaxis is the administration of antibiotics after suspected exposure to plague has occurred but before symptoms are present. If symptoms are present, see section above on treatment. Persons thought to have had an infective exposure should receive post-exposure prophylaxis. Infective exposures include household, hospital, or other close contact (less than 2 meters) with a person suspected or confirmed to have pneumonic plague who has received no treatment, less than 48 hours of antimicrobial therapy, or more than 48 hours of antimicrobial therapy without clinical improvement. Post-exposure prophylaxis may be recommended for persons exposed to intentional aerosol releases. In such an event, public health authorities will provide guidance. Regardless of whether post-exposure prophylaxis is recommended or taken, persons potentially exposed should be observed for fever or cough for 7 days after exposure. Any potentially-exposed person who develops a fever or cough should seek prompt medical attention and begin treatment. Quarantine is not currently recommended.[4, 7, 9]

Vaccination

Current killed whole cell vaccines have been in use for military personnel and have been shown to generate cell-mediated responses lasting at least 15 years; however, they require repeat dosing with adjuvants, have questionable protection against respiratory infections, and are reactogenic. Vaccine production has been discontinued in the US. Microencapsulated subunit vaccines (of F1 and V proteins) requiring only single dose administration are under development and show the most promise against aerosol exposures.[4, 38, 39]

COMPLICATIONS AND ADMISSION CRITERIA

Whereas primary pneumonic plague results from direct inhalation of plague bacilli, secondary pneumonic plague can manifest as a complication in patients with bubonic plague. Hematogenous dissemination of *Y. pestis* results in plague septicemia, which can be complicated by septic shock, disseminated intravascular coagulation, necrosis of small vessels, and purpuric skin lesions. Plague meningitis due to hematogenous seeding of the meninges occurs infrequently.

Patients with suspect or confirmed pneumonic or bubonic plague require hospitalization for intravenous antibiotics, supportive care, and close monitoring for decompensation and signs of toxemia.

INFECTION CONTROL

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfcdcp.org).

Clinicians should notify local public health authorities, their institution's infection control professional and their laboratory of any suspected plague cases. Public health authorities may conduct epidemiological investigations and implement disease control interventions to protect the public. Infection control professionals will guide and enforce implementation of infection control precautions within the healthcare setting. Laboratory personnel will take appropriate biosafety precautions.

Although not highly contagious, plague can be transmitted person-to person via respiratory droplets when the disease is end stage.[30] Both the Healthcare Infection Control Practices Advisory Committee of the CDC and the Working Group on Civilian Biodefense recommend **Droplet and Standard precautions** for patients with suspected or confirmed pneumonic plague. These precautions should be maintained until 48 hours of appropriate antibiotics have been administered AND the patient shows clinical improvement. Close contacts of pneumonic plague patients should be identified, assessed for prophylaxis and monitored for symptoms. For patients with suspected or confirmed bubonic plague or other non-pneumonic plague syndromes, **Standard precautions** are recommended. Aerosol-generating procedures should be avoided if possible. Routine laboratory procedures should be carried out under Biosafety level-2 conditions; however, manipulation of cultures or other activities that may produce aerosol or droplets (e.g., centrifuging, grinding, vigorous shaking, and animal studies) require Biosafety level -3 conditions.[4, 40]

Decontamination

In general, environmental decontamination following an aerosol event has not been recommended, since experts have estimated that an aerosol of *Y. pestis* organism would be infectious for only about 1 hour.[4, 40] A recent study demonstrated that *Y. pestis* can survive on selected environmental surfaces for at least several days; however the potential for re-aerosolization of these organisms was not addressed.[41] Commercially available bleach or 0.5% hypochlorite solution (1:10 dilution of household bleach) is considered adequate for cleaning and decontamination. All persons exposed to an aerosol containing *Y. pestis* should be instructed to wash body surfaces and clothing with soap and water.

PEARLS AND PITFALLS

- Bubonic plague is not transmitted directly from one human to another in the absence of lymph node suppuration and drainage. Persons with bubonic plague become more infectious as *Y. pestis* organisms reach the lungs via hematogenous spread. Once pneumonic plague develops, transmission occurs via direct contact with respiratory secretions or inhalation of respiratory droplets.

- Clinical clues pointing toward a diagnosis of primary pneumonic plague are sudden onset of headache, malaise, and fever, fulminant pneumonitis with rapid progression from dry cough to tachypnea, dyspnea, and productive cough, and in the late stage of disease, hemoptysis with copious amounts of bright red sputum.[30]

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SMALLPOX

Outline

Immediately report any suspected or confirmed cases of smallpox to:
SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830)

- By law, health care providers must report suspected or confirmed cases of smallpox to their local health department immediately [within 1 hr].
- SFDPH Communicable Disease Control can facilitate specialized testing and will initiate the public health response as needed.

Also notify your:

- Infection Control Professional
- Clinical Laboratory

INTRODUCTION

Smallpox is caused by variola viruses, which are large, enveloped, single-stranded DNA viruses of the Poxvirus family and the *Orthopoxvirus* genus. Variola major strains cause three forms of disease (ordinary, flat type, and hemorrhagic), whereas variola minor strains cause a less severe form of smallpox. Vaccination with vaccinia virus, another member of the *Orthopoxvirus* genus, protects humans against smallpox because of the high antibody cross-neutralization between orthopoxviruses.[1-4]

The Working Group for Civilian Biodefense considers smallpox to be a dangerous potential biological weapon because of "its case-fatality-rate of 30% or more among unvaccinated persons and the absence of specific therapy." Of the potential ways in which smallpox could be used as a biological weapon, an aerosol release is expected to have the most severe medical and public health outcomes because of the virus' stability in aerosol form, low infectious dose, and high rate of secondary transmission. A single case of smallpox would be a public health emergencey.[2]

EPIDEMIOLOGY

Smallpox as a Biological Weapon

Smallpox has been used as a biological weapon in the distant past. More recently it has been a focus of bioweapons research. In the 18th century, British troops in North America gave smallpox-infected blankets to their enemies, who went on to suffer severe outbreaks of smallpox. Defecting Russian scientists describe covert Russian operations during the 1970s and 1980s that focused on

bioweapons research and development including creation of more virulent smallpox strains and development of missiles and bombs that could release smallpox.[2, 4, 5]

Aerosol release of virus (such as into a transportation hub) would likely result in a high number of cases. Other possibilities include use of "human vectors" (i.e., persons who have been deliberately infected with smallpox) and use of fomites (e.g., contamination of letters sent through the mail).[2, 5]

Smallpox is of concern as a biological weapon because:[2]

- much of the population (80%) is susceptible to infection
- the virus has a low infectious dose and carries a high rate of morbidity and mortality
- a vaccine that lacs significant side effects is not yet available for general use
- experience has shown that introduction of the virus creates havoc and panic

An intentional release of smallpox would have the following characteristics:[6]

- Clustering in time: Multiple similarly presenting cases of fever and rash in mouth and on face, arms, and legs generally 4 days after release

Naturally Occurring Smallpox

Reservoirs

The natural reservoir for smallpox was humans with disease; there was no chronic carrier state. In 1980, the World Health Organization (WHO) declared smallpox eradicated from the world and recommended destruction or transfer all remaining stocks to one of two WHO reference labs, the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, and the former Institute of Virus Preparations (later transferred to the Vector Institute) in Russia. Since eradication, there is no natural reservoir for smallpox. Presently, smallpox is only officially found in these designated WHO reference laboratories.[2, 5, 6]

Mode of Transmission

Historically, humans were able to be infected in a number of ways:[1, 2, 6]

- Inhalation of droplet nulcei or aerosols originating from the mouth of smallpox-infected humans
- Direct contact with skin lesions or infected body fluids of smallpox-infected humans
- Direct contact with contaminated clothing or bed linens

Worldwide occurrence

In 1967, a WHO-led international campaign of mass vaccination, surveillance and outbreak containment was started in order to eradicate smallpox globally. In 1977, the last community-acquired smallpox case was reported in Somalia, and in 1978, a laboratory accident in England caused the last human case.[3]

Occurrence in the United States

The last case of smallpox in the United States occurred in the Rio Grande Valley of Texas in 1949. The risk of disease was low enough to end routine vaccination of the US population in 1971.[3]

Vaccination is currently required for most military personnel and is recommended for select health care and emergency workers, described below. Because of the relative frequency and seriousness of vaccine-related complications and the low risk of smallpox outbreak in the United States, routine vaccination is not recommended for the vast majority of healthcare workers or for the general U.S. population.[7]

In 2002, the CDC recommended pre-event vaccination for local smallpox response teams, consisting of public health, medical, nursing, and public safety personnel, who would conduct investigation and management of initial smallpox cases. As of July 31, 2004, 39,608 healthcare workers and first responders had been vaccinated nationally.[6]

CLINICAL FEATURES

Historically, smallpox has been divided into variola major and variola minor based on severity of clinical disease. Variola major was more common and caused more severe disease relative to variola minor. The case mortality was 15 to 45% for variola major and 1% for variola minor.

The infectious dose for smallpox is a few virions. The virus typically enters the body via respiratory or oral mucosa and is carried by macrophages to regional lymph nodes from which a primary asymptomatic viremia develops on the 3rd or 4th day after infection. The reticuloendothelial organs are invaded and overwhelmed leading to a secondary viremia around the 8th to 12th day after infection. Toxemia and fever onset follow. Seven to 17 days following infection, fever, malaise, and extreme exhaustion begin. A maculopapular rash first presents on the face, mouth, pharynx, and forearms and spreads to the trunks and legs. The rash progresses to a vesicular and pustular stage (round and deeply embedded). Scabs form on the 8th day of the rash. Scars are formed from sebaceous gland destruction and granulation tissue shrinking and fibrosis.[1-4, 6]

Although most data supports communicability with rash onset, some low level of communicablity is present prior to rash onset because viral shedding from oral lesions occurs during the 1 to 2 days of fever preceding rash onset. However, secondary transmission peaks 3 to 6 days after fever onset (1st week after rash onset), and 91.1% of secondary cases occurred by the 9th day after fever onset.[8] The period of communicability ends when all the scabs have fallen off. Scabs are not very infectious because the tight binding of the fibrin matrix retains the virions; however secondary cases have been documented through transmission from direct contact with contaminated clothing and bedding.[1-4, 6]

Secondary bacterial infection and other organ involvement are uncommon. Encephalitis is a possible complication. Mortality is most commonly associated with toxemia of circulating immune complexes and soluble variola antigens and is seen in the second week of illness. Approximately 30 to 80% of unvaccinated close contacts will develop the disease. In addition, 3.5 to 6 transmissions per smallpox case are estimated.[6]

Variola Major

Variola major is associated with the most severe disease, and presents as:

- ordinary (80% or more of cases: mortality is 30% in unvaccinated and 3% in vaccinated patients)
- flat (4 to 6% of cases: mortality is 95% in unvaccinated and 66% in vaccinated patients)
- hemorrhagic (2 to 3% of cases: mortality is 99% in unvaccinated and 94% in vaccinated patients)
- modified (13% of cases and low risk of death)
- variola sine eruptione (30 to 50% of vaccinated contacts of smallpox and low risk of death)

CLINICAL FEATURES: ORDINARY VARIOLA MAJOR.[1-4, 6]	
Incubation Period	10-13 days (range 7-19 days)
Transmission	• Inhalation of droplet nuclei or aerosols originating from the mouths of smallpox-infected humans • Direct contact with skin lesions or infected body fluids of smallpox-infected humans • Direct contact with contaminated clothing or bed linens
Signs and Symptoms	Prodromal phase • 2-4 days of fever, chills, headache, backache, and often GI symptoms Rash phase • Enanthem (papules, vesicles, then ulcers) of oropharyngeal mucosa beginning 1 day before skin lesions appear • First skin lesions ("herald spots") are often on the face • Lesions spread centrifugally: trunk to proximal extremities to distal extremities • Palms and soles are usually involved, and truncal rash is usually sparse • Lesion progression: maculopapular (days 1-2), vesicular (days 3-5), pustular (days 7-14) • Vesicles and pustules are frequently umbilicated • Pustules can be like small, embedded hard balls or "shotty" • Lesions tend to progress at same rate • Lesions may be discrete, semiconfluent, or confluent • Lesions are typically painful and cause pitted scars as they heal • Lesions gradually scab over during days 13-18
Progression and Complications	• Viral bronchitis or pneumonitis • Third spacing of fluid with resulting electrolyte and renal abnormalities • Skin desquamation • Secondary bacterial infection, particularly skin and pulmonary • Spontaneous abortion, stillbirth • Rarely: blindness, keratitis, corneal ulceration, encephalitis, osteomyelitis or arthritis, orchitis • Death may occur during 2nd week of illness, from high-level viremia and circulating immune complexes
Laboratory Findings	• Lymphocytopenia and/or granulocytopenia

GI, gastrointestinal

Other forms of smallpox caused by variola major infection include:

Flat-type smallpox (also known as **malignant smallpox**) occurred in about 4 to 6% of cases and more frequently in children. It is associated with a late, deficient cellular immune response. It is characterized by a short incubation period, prostrating prodromal illness, severe systemic toxicity and high mortality (90-97%). The lesions do not progress to the pustular stage, instead remaining soft, velvety and flattened. If the patient survives, the lesions will resolve by desquamation without scabs or scarring.

Hemorrhagic smallpox occurred in about 2 to 3% of cases. Pregnant women are highly susceptible. Similar to flat-type smallpox, it is associated with a defective immune response. It is characterized by a short incubation period, prostrating prodromal illness, severe systemic toxicity, and high mortality (96%). The rash begins as a dusky erythema, followed by extensive petechiae, mucosal hemorrhage, and intense toxemia. Thrombocytopenia and coagulopathy may be present. These patients usually died during week 1 of illness, often before the development of the typical pox lesions.

Modified smallpox occurred in about 13% of cases. It occurred in persons with some immunity. The pre-eruptive illness is typical in duration and severity as ordinary smallpox; however, during the eruption, fever is absent and the skin lesions are superficial, pleomorphic, fewer in number, and evolve rapidly.

Variola sine eruption occurred in about 30 to 50% of vaccinated contacts of smallpox cases. It is characterized by a sudden onset of fever, headache, occasional backache which resolves within 48 hours, influenza-like symptoms and no rash.

Variola Minor

Variola minor, caused by different strains of variola, is a milder form of smallpox. Compared with variola major, there are milder constitutional symptoms, discrete lesions that evolve a bit more rapidly, lower rates of hemorrhagic disease, and only rare fatal outcomes (<1%). The illness may be difficult to distinguish clinically from modified smallpox and variola without eruption. In the 1890s, variola minor spread from South Africa to Florida. In the early 1900s, variola minor became prevalent in the United States, Latin America, and Europe.

DIFFERENTIAL DIAGNOSIS

The characteristic features of smallpox need to be differentiated from other illnesses that present with vesicular or pustular rash. One disease that could be confused with smallpox is chickenpox. These may be differentiated clinically, as follows:

CLINICAL DIFFERENTIATION OF VARIOLA VS. VARICELLA[9]		
Feature	**Variola**	**Varicella**
Prodrome	• Duration: 2-4 days • Fever, chills, headache, backache, often GI symptoms	• Commonly does not occur • If present, mild symptoms and duration of 1 day
Rash Distribution	• Centrifugal: more dense on face and distal extremities • Frequently involves palms and soles • More involvement of back than abdomen	• Centripetal: more dense on trunk • Spares palms and soles • Back and abdomen equally involved
Lesion Evolution	• Usually appear on oropharyngeal mucosa first, then all over within 1-2 days • Progress at same rate; at any point in time, lesions are at same stage of evolution • Lesions progress slowly (7-14 days) from macules to papules to vesicles to pustules to scabs	• Lesions appear in crops • At any point in time, crops of lesions are at different stages of evolution • Lesions progress quickly (1-2 days) from macules to papules to vesicles to scabs
Lesion Attributes	• May be semiconfluent or confluent • Deep • May be umbilicated • Often painful; pruritic only as scabs	• Usually discrete • Superficial • Rarely found of palms and soles • Do not umbilicate or dimple • Typically painless; intensely pruritic
GI, gastrointestinal		

Monkeypox is another disease that could be confused with smallpox. In 2003, an outbreak of monkeypox, associated with prarie dog contact, took place in the midwestern United States. Monkeypox in humans presents similarly to ordinary smallpox. However, monkeypox is milder and has prominent lymphadenopathy and a shorter duration of rash.

The CDC has outlined criteria for determining the risk of smallpox when evaluating patients with generalized vesicular or pustular rash:[9, 10]

Risk of Smallpox in Patients with Generalized Vesicular or Pustular Rash	
High	All three major criteria present: a) Febrile prodrome 1-4 days before rash onset, with fever >101°F, plus 1 or more of the following: prostration, headache, backache, chills, vomiting, severe abdominal pain b) Classic smallpox lesions present (vesicles or pustules that are deep-seated, firm or hard, round, and well-circumscribed; sharply raised and feel like BB pellets under the skin; may become umbilicated or confluent as they evolve) c) Lesions on any one part of the body are in the same stage of development
Moderate	Febrile prodrome as in (a) above, plus either (b) or (c) above

	OR Febrile prodrome as in (a) above, plus at least four of the following minor criteria: • Centrifugal distribution • First lesions appeared on the oral mucosa/palate, face, or forearms • Patient appears toxic or moribund • Slow evolution of lesions from macules to papules to pustules over several days • Lesions on the palms and soles
Low	No viral prodrome *OR* Febrile prodrome as in (a) above, plus < 4 minor criteria above

Additional considerations in the differential diagnosis of smallpox include:

Macular/papular stage

- measles
- scarlet fever
- rubella

Vesicular/pustular stage:

- disseminated herpes zoster
- disseminated herpes simplex
- Mmolluscum contagiosum
- bullous pemphigoid
- impetigo (*Streptococcus, Staphylococcus*)
- human monkey pox

Either stage:

- erythema multiforme major - (Stevens-Johnson syndrome)
- miscellaneous drug eruptions
- secondary syphilis
- enteroviral infection (hand, foot & mouth disease)
- chickenpox
- contact dermatitis
- generalized vaccinia
- acne
- scabies/insect bites

Hemorrhagic smallpox may resemble:

- meningococcemia
- rickettsial infections
- Gram-negative septicemia

Flat-type smallpox may resemble:

- hemorrhagic chickenpox

LABORATORY DIAGNOSIS

The diagnosis of smallpox requires a high index of suspicion because the disease has been eradicated and its clinical presentation is similar to other pox viruses. Routine laboratory findings for specific clinical presentations of smallpox are listed in the clinical features table. Radiographic findings do not assist in identification of smallpox.

If you are testing or considering testing for smallpox, you should:

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830).** SFDPH can authorize and facilitate testing, and will initiate the public health response as needed.
- **Inform your lab that smallpox is under suspicion.**

Diagnosis of smallpox will be clinical initially, but followed by laboratory confirmation. Once smallpox has been confirmed in a geographic area, additional cases can be diagnosed clinically, and specimen testing can be reserved for specific cases in which the clinical presentation is unclear or to assist with law enforcement activities.

Clinicians should use the CDC-developed tools to assess the likelihood that patients with acute generalized vesicular or pustular rash illnesses have smallpox.[9] CDC has also developed algorithms for laboratory evaluation of suspect smallpox cases based on the likelihood of disease.[10] If a patient is determined to be at high risk for smallpox, clinicians should call their local public health authorities immediately and obtain photos of the patient. Public health will provide guidance on specimen collection and packaging and will facilitate transport of specimens to the appropriate public health laboratory.

Multiple tests will be used to evaluate for smallpox. Polymerase chain reaction (PCR) testing will be an important method; however, other methods will also be used including: electron microscopic examination of vesicular or pustular fluid or scabs, direct examination of vesicular or pustular material looking for inclusion bodies (Guarnieri's bodies), culture on egg chorioallantoic membrane, tissue culture, strain analysis with a restriction fragment length polymorphism assay, and serology. Definitive laboratory identification and characterization of the variola virus requires several days.

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfcdcp.org).

Treatment

The management of confirmed or suspected cases of smallpox consists of supportive care, with careful attention to electrolyte and volume status, and ventilatory and hemodynamic support. General supportive measures include ensuring adequate fluid intake (difficult because of the enanthem), alleviation of pain and fever, and keeping skin lesions clean to prevent bacterial superinfection. [1-4, 6]

Currently there are no FDA approved antiviral agents with proven activity against smallpox in humans.

Antiviral agents that have shown some activity in vitro against poxviruses may be available from the CDC under an investigational protocol. ST-246 is a novel agent that is currently undergoing safety and efficacy testing.[6, 11] Additionally, cidofovir, a nucleoside analogue DNA polymerase inhibitor, might be useful if administered within 1-2 days after exposure; however, there is no evidence that it would be more effective than vaccination, and it has to be administered intravenously and causes renal toxicity.

Immunity from prior vaccination

Protection from smallpox is estimated to last between 11.7 to 28.4 years after primary vaccination and longer for variola minor than for variola major. Those who were previously vaccinated may retain some protection that could decrease the severity of the disease and allow for greater mobility thereby complicating public health response.[12]

Postexposure prophylaxis

Postexposure prophylaxis for smallpox is the administration of vaccinia vaccine after suspected exposure to smallpox has occurred but before symptoms are present. Immunity generally develops within 8 to 11 days after vaccination with vaccinia virus. Because the incubation period for smallpox averages about 12 days, vaccination within 4 days may confer some immunity to exposed persons and reduce the likelihood of a fatal outcome. Postexposure vaccination may be particularly important for those vaccinated in the past, provided that revaccination is able to boost the anamnestic immune response. In addition to vaccination, exposed persons should be monitored for symptoms. Temperature should be checked once a day, preferably in evening, for 17 days after exposure for fever (over 38°C).[2-4, 6, 7]

If a case or cases of smallpox occur, public health authorities will conduct surveillance and implement containment strategies. Ring vaccination will be important and includes identification of contacts of cases and provision of prophylaxis and guidance on monitoring for symptoms. Large-scale voluntary vaccination may be offered to low-risk populations to supplement and address public concerns.

Vaccine Supply, Administration, and Efficacy

The smallpox vaccine used in the United States (formerly Dryvax, now ACAM2000) is a lyophilized (freeze-dried) preparation of live attenuated vaccinia virus, an *Orthopoxvirus* closely related to cowpox that induces antibodies that are protective against smallpox. The ACAM2000 uses vaccinia virus derived from the Dryvax vaccine via plaque purification cloning. The virus is then grown in African green monkey (Vero) cells. The ACAM2000 preparation also contains HEPES, human serum albumin, mannitol and trace amounts of neomycin and polymixin B. The diluent contains glycerin and a phenol preservative.[13]

Production of the Dryvax vaccine stopped in the 1980s. Acambis currently makes the ACAM2000 vaccine which received FDA approval in September 2007. By that time 192.5 million doses of ACAM2000 were already in the United States stockpile. All lots of Dryvax vaccine expired February 20, 2008, and were destroyed by March 31, 2008.[6, 14]

Technique. The Dryvax vaccine should be administered by trained, vaccinated personnel using a bifurcated needle that is stroked against the skin until blood appears. Vaccinees are instructed to

keep the site dry and covered, to avoid touching the site, and to thoroughly launder or carefully discard any materials that come into contact with the site. **Should smallpox vaccination be deemed necessary, it will be coordinated by local, state and federal health agencies.** For additional information on vaccine administration, see http://www.bt.cdc.gov/agent/smallpox/vaccination. [7]

Vaccine Contraindications and Complications

The ACAM2000 and Dryvax vaccines have similar safety profiles.[14] Both have serious complications. Likelihood of adverse effects is 3 to 4-fold higher in infants and in primary recipients. Based on the U.S. Vaccine Adverse Events Reporting System of recently vaccinated people, there was a rate of 26.4 deaths per 10,000 vaccinees. Adverse events included the following: 33% cardiac, 25% nonspecific chest pain, 21% neurological, 14% infection, 3% malignancy, 3% pulmonary (noninfectious), and 1% normal vaccination response.[13, 15, 16]

Vaccination during the pre-exposure period is contraindicated for certain persons. **During a smallpox emergency, however, all contraindications would be reviewed in the context of the risk of smallpox exposure, and updated recommendations would be issued by public health authorities.** Current contraindications to vaccination are as follows (see www.bt.cdc.gov/agent/smallpox/vaccination for further description):[7, 13]

- past or present eczema or atopic dermatitis (risk of eczema vaccinatum)
- other acute or chronic exfoliative skin conditions (e.g. burns, impetigo, chicken pox, contact dermatitis, shingles, herpes, severe acne, psoriasis), until the condition resolves
- immunodeficiency states, due to disease or treatment of disease
- pregnancy (vaccination may offer partial protection for mother, but increases risk of fetal vaccinia)
- breastfeeding
- hypersensitivity to vaccine components
- under 18 years of age in nonemergency situations
- having a household contact who is immunodeficient, who has past or present eczema or atopic dermatitis, or who has an acute, chronic, or exfoliative skin condition
- physician-diagnosed cardiac disease, or 3 or more major risk factors for cardiac disease

Well-documented adverse reactions to vaccination are listed below:[1, 2, 7, 13]

- tenderness, erythema, or other localized reactions at the injection site
- systemic symptoms of fever, malaise, myalgias, local lymphadenopathy
- dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, urticaria, exanthems, contact dermatitis, and erythematous papules
- secondary bacterial infections at injection site
- focal and generalized suppurative folliculitis (without evidence of viral infection; may be mistaken for generalized vaccinia)
- inadvertent autoinoculation of another body site (most common sites are face, eyelid, nose, mouth, genitalia, rectum)
- generalized vaccinia: vesicles or pustules appearing distant from the vaccination site

- eczema vaccinatum: localized or dissemination of vaccinia virus; usually mild but may be severe and fatal
- vaccinia keratitis
- progressive vaccinia: progressive necrosis in vaccination area, often with metastatic sites; can be severe and fatal
- postvaccinial encephalitis
- fetal vaccinia: occurs when mother is vaccinated during during pregnancy; usually results in premature birth or miscarriage
- myopericarditis, identified among military personnel vaccinated between December 2002 and December 2003
- death: 1.1 deaths per 1 million primary vaccine recipients
- contact vaccinia: transmission of vaccinia virus from newly vaccinated persons to susceptible unvaccinated contacts

The primary therapy for adverse reactions to smallpox vaccination is vaccinia immunoglobulin (VIG).[7] However VIG is contraindicated in vaccinia keratitis and provides no benefit in postvaccinial encephalitis. VIG is manufactured from the plasma of persons vaccinated with vaccinia vaccine. An intravenous preparation (VIGIV) was recently licensed by the FDA.[17] Cidofovir and topical ophthalmic antiviral agents are also recommended by some experts.[7] Cidofovir use requires an Investigational New Drug (IND) protocol, and topical ophthalmic agent use is off-label.

COMPLICATIONS AND ADMISSION CRITERIA

Before smallpox was eradicated worldwide, viral bronchitis and pneumonitis were the most frequent complications of ordinary-type smallpox. Cutaneous complications included desquamation, massive subcutaneous fluid accumulation with electrolyte abnormalities and renal failure, or, less commonly, secondary bacterial infection of smallpox lesions. Infrequently, smallpox patients experienced encephalitis, osteomyelitis, corneal ulceration, or ocular keratitis. Ordinary-type smallpox with confluent lesions, rather than discrete lesions, carried a much higher risk of massive exfoliation, tissue destruction, bacterial sepsis, and death. Hemorrhagic-type and flat-type smallpox were nearly always fatal.[1-4, 6]

Many patients do not require hospitalization. Those with discrete lesions, nonhemorrhagic and non-flat-type, are less likely to become critically ill or require much supportive care and can be more easily managed outside the hospital. These people should be isolated and monitored at home or in a nonhospital facility, and smallpox vaccination should be provided to caregivers and household members. Patients with evidence of severe disease or presentations that suggest progression to severe disease is likely should be considered for admission to a negative-pressure environment with strict maintenance of Airborne Precautions.[2, 6]

INFECTION CONTROL

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfcdcp.org).

Clinicians should notify local public health authorities, their institution's infection control professional, and their laboratory of any suspected smallpox cases. Public health authorities may conduct epidemiological investigations and will implement disease control interventions to protect the public. Infection control professionals will implement infection control precautions within the healthcare setting. Laboratory personnel should take appropriate safety precautions.

Smallpox is transmissible from person to person by exposure to respiratory secretions and by direct contact with pox lesions and fomites. **Airborne and Contact Precautions** in addition to **Standard Precautions** should be implemented for patients with suspected smallpox and until all scabs have separated. Healthcare workers caring for patients with suspected smallpox should be vaccinated immediately.[18, 19]

Decontamination

Survival of the virus in the environment is inversely proportional to temperature and humidity. All bedding and clothing of smallpox patients should be minimally handled to prevent re-aerosolization and autoclaved or laundered in hot water with bleach. Standard disinfection and sterilization methods are deemed to be adequate for medical equipment used with smallpox patients and cleaning surfaces and rooms potentially contaminated with the virus. Airspace decontamination (fumigation) is not required.[2, 19]

PEARLS AND PITFALLS

1. The CDC has developed a number of clinical diagnostic tools to assist with the visual recognition, differential diagnosis, and initial management of suspected smallpox. These resources are available at: http://www.bt.cdc.gov/agent/smallpox/index.asp. [20]

2. Hemorrhagic smallpox is rare but can be confused with invasive meningococcal disease, rickettsial infections, or gram-negative sepsis because of the patient's ill appearance, petechial and purpuric lesions, and hemorrhagic manifestations.

3. Smallpox is most often transmitted through direct contact with respiratory droplets as a result of close (within 2 meters) or face-to-face contact. Viruses can also travel over greater distances as airborne particles, particularly in cases with coughing. Transmission has occasionally been linked to fomites carried on clothing or bedding that has been contaminated by dried respiratory secretions or draining skin lesions.

4. Since 2003, many health departments have established smallpox preparedness teams consisting of providers who have been pre-vaccinated against smallpox who can asssist with the response to a suspected case of smallpox.

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TULAREMIA

JULY 2008

Outline

Immediately report any suspected or confirmed cases of tularemia to:

SFDPH Communicable Disease Control
(24/7 Tel: 415-554-2830)

- By law, health care providers must report suspected or confirmed cases of tularemia to their local health department immediately [within 1 hr].
- SFDPH Communicable Disease Control can facilitate specialized testing and will initiate the public health response as needed.

Also notify your:

- Infection Control Professional
- Clinical Laboratory

INTRODUCTION

Tularemia is a zoonotic disease caused by *Francisella tularensis*, a non-sporulating, non-motile, aerobic, gram-negative coccobacillus. There are multiple subspecies of *F. tularensis,* with the biovars *tularensis* (type A) and *holarctica* (type B) occurring most commonly in the United States. The clinical syndromes caused by tularemia depend on the route of infection and subspecies of the infecting organism. Tularemia is highly infectious, requiring inhalation or inoculation of as few as 10 to 50 organisms to cause disease.[1] Although its virulence factors are not well characterized, type A is generally thought to be the more virulent subspecies.[2-4] However, the virulence of type A subspecies may vary between geographic regions within the US, with the mid-western and eastern states having more severe infections.[5, 6]

The Working Group for Civilian Biodefense considers tularemia to be a dangerous potential biological weapon because of its "extreme infectivity, ease of dissemination, and its capacity to cause illness and death." Of the potential ways that *F. tularensis* could be used as a biological weapon, an aerosol release is expected to have the most severe medical and public health outcomes.[3]

EPIDEMIOLOGY

Tularemia as a Biological Weapon

Weaponized *F. tularensis* was developed and stockpiled by the US military, though the supply was destroyed in the 1970's. The Soviet Union is reported to have developed antibiotic- and vaccine-resistant strains of weaponized *F. tularensis*.[3]

Experts believe that an aerosolized release is the most likely intentional use of *F. tularensis* organisms. Exposure to aerosolized *F. tularensis* would cause:[2]

- Via inhalation:
    - primary pneumonic tularemia (majority of patients)
    - typhoidal tularemia (nonspecific febrile illness of varying severity)
    - oropharangeal tularemia
- Via contact with eyes: oculoglandular tularemia
- Via contact with broken skin: glandular or ulceroglandular disease

An intentional release of tularemia would have the following characteristics:

- Multiple similarly presenting cases clustering in time:
    - acute non-specific febrile illness with onset 3 to 5 days after the initial release (range 1-14 days)
    - community-acquired atypical pneumonia unresponsive to typical antimicrobials
- Atypical host characteristics: unexpected, unexplained cases of acute illness in previously healthy persons who rapidly develop pleuropneumonia and systemic infection, especially if patients develop pleural effusions and hilar lymphadenopathy
- Unusual geographic clustering: multiple cases in an urban area, where naturally occurring tularemia is not endemic
- Absence of risk factors: patients lack tularemia exposure risk factors (e.g. outdoor field work or recreational activity, contact with tissues of potentially infected animals)

Intentionally released *F. tularensis* strains may be altered to have enhanced virulence or antimicrobial resistance.[3]

Naturally Occurring Tularemia

Reservoir

The natural reservoirs for *F. tularensis* are small and medium-sized mammals. In the United States these are primarily lagomorphs (rabbits, hares) but may include beaver, squirrels, muskrats, field voles, and rats. Incidental hosts include some species of mammals (e.g. humans, cats, dogs, cattle), birds, fish, and amphibians. Organisms can survive for weeks in moist environments, including water, mud, and decaying animal tissue.[2] There is some evidence that the protozoa *Acanthamoeba castellanii*, may be an important reservoir for F. tularensis.[7]

Mode of Transmission

The primary vectors for infection in the United States are ticks (dog ticks, wood ticks) and flies, such as the deerfly. Humans become infected by a number of mechanisms:[3]

- bites by infected arthropods (majority of cases)
- contact with infectious animal tissues or fluids, during for example hunting or butchering
- ingestion of contaminated food, water, or soil
- inhalation of infectious aerosols, including aerosols generated during landscaping activities (e.g., lawn mowing, using a power blower, and brush cutting)

- exposure in the laboratory (accidental inhalation of aerosol, direct contact with an infectious specimen including accidental parenteral inoculation, or ingestion)

Tularemia is not spread from person to person.

Worldwide Occurrence

Worldwide, human cases of tularemia occur throughout North America, Europe, and Asia. Infections with type A strain are generally only seen in North America. Within Europe and Asia, the greatest numbers of human cases are reported in Scandinavian countries and countries of the former Soviet Union.[3] Recent significant outbreaks of tularemia in humans include: Sweden (2000, 2003, 2006), Kosovo (2002), France (2004), Turkey (2004-2005), Bulgaria (1997-2005) and Spain (2007).[2, 8-10]

United States Occurrence

Nationwide, incidence of tularemia has declined from approximately 2000 annually reported cases during the first half of the 20th century to an average of 124 cases per year during the 1990s. Most cases occur in rural or semirural environments, during the summer months, with the greatest number of cases occurring in Missouri, Oklahoma, South Dakota, Montana, and Martha's Vineyard, Massachusetts. From 1990 to 2000, incidence of tularemia in the United States was highest in children 5-9 years and adults 75 years and older. Regardless of age, males had a higher incidence of tularemia, potentially because of participation in activities more likely to cause exposures, such as hunting, trapping, butchering, and farming.[11]

Recent significant outbreaks include:

- In 1978 and 2000, outbreaks of the rare primary pneumonic tularemia occurred on Martha's Vineyard, Massachusetts. These represent the only outbreaks of primary pneumonic tularemia in the United States. Additional cases of tularemia have been reported each year in Martha's Vineyard (2000-2006). Exposure is most likely from breathing infectious aerosols generated during landscaping activities.[12] The reservoir in these outbreaks is still unclear, but may involve skunks and raccoons.[13]
- In 2002, tularemia was responsible for a die-off of several hundred prairie dogs caught in the wild in South Dakota and then commercially distributed widely throughout the USA. One human case occurred in an animal handler who cared for the infected animals.[14]
- In 2003, low levels of *F. tularensis* were identified in a biodetection air-monitoring system in Houston, Texas. No human cases occurred. An investigation supported contamination of the filters by naturally occurring *F. tularensis* organisms from an unidentified environmental reservoir.[15]

Occurrence in California and San Francisco

From 2000 to 2007, 16 cases of plague were reported in California, and one of these occurred in San Francisco.[16-19]

CLINICAL FEATURES

Human tularemia occurs in six recognized forms, determined primarily by route of infection. Tularemia infection can range from mild to severe clinical illness and can be life-threatening.

Overall case-fatality rates have declined from 5-15% in the pre-antibiotic era to approximately 2% currently. Mortality was historically much higher with pneumonic and typhoidal tularemia, with case-fatality as high as 30-60% if untreated.[3] Administration of appropriate antibiotic treatment typically leads to general symptom improvement within 24-48 hours. Recognition of tularemia as a potential etiologic agent is critical, because poor outcomes have been associated with delays in seeking care and/or instituting effective antimicrobial treatment.[20]

Pneumonic Tularemia

Pneumonic tularemia causes the most severe disease, and presents as a non-specific febrile illness with progression to pleuropneumonitis and systemic infection.

PNEUMONIC TULAREMIA	
Incubation Period	3-5 days (range 1-14 days)
Transmission	• Inhalation of contaminated aerosols • Secondary hematogenous spread to the lung
Signs and Symptoms	• Initial presentation as atypical CAP unresponsive to routine antibiotic therapy, which can progress slowly OR rapidly to severe disease • Fever (abrupt onset), headache, cough, minimal or no sputum production, dyspnea, pleuritic chest pain, myalgias (often prominent in lower back), bronchiolitis and/or pharyngitis may be present • Generalized maculopapular rash with progression to pustules or erythema-nodosum type rash occurs in 20% • Nausea, vomiting, diarrhea is not uncommon • Hemoptysis (not common)
Progression and Complications	• Respiratory failure, ARDS • Severe pneumonia • Lung abscess or cavitary lesions • Sepsis
Laboratory Findings	• Lobar, segmental, or subsegmental opacities on CXR, pleural effusion, pleural adhesions, Hilar adenopathy • Leukocytosis; differential may be normal • Liver enzymes and/or CK may be abnormal • Sputum gram stain usually nonspecific
ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; CK, creatine kinase; CXR, chest x-ray.	

Glandular and Ulceroglandular Tularemia

Glandular and ulceroglandular tularemia account for the majority of naturally occurring cases of tularemia. In the *ulceroglandular* form, an ulcer is formed at the site of inoculation, with subsequent lymphadenopathy in the proximal draining lymph nodes. Occasionally, lymphadenopathy occurs without an ulcer, leading to the designation of *glandular* disease.

GLANDULAR AND ULCEROGLANDULAR TULAREMIA	
Incubation Period	3-5 days (range 1-14 days)
Transmission	• Bite of an infective arthropod • Direct contact with infectious material (i.e., contaminated carcass, settled infectious aerosol)
Signs and Symptoms	• Ulceroglandular form – local skin involvement at site of exposure that develops into a painful cutaneous papule with subsequent ulceration within several days. Papule becomes necrotic and scars. • Glandular form – no cutaneous lesion occurs • Enlarged and tender regional lymphadenopathy that can persist for months • Fever, chills, malaise, myalgias, arthralgias, headache, anorexia, GI symptoms are common
Progression and Complications	• Lymph node suppuration • Secondary pneumonia • Hematogenous spread to other organs • Sepsis
Laboratory Findings	• Leukocytosis; differential may be normal • Liver enzymes and/or CK may be abnormal
CK, creatine kinase; GI, gastrointestinal.	

Oculoglandular Tularemia

Oculoglandular tularemia results either from ocular inoculation from the hands after contact with contaminated material or from splashes or aerosols generated during handling of infective material (e.g., animal carcasses). This form of tularemia could occur in a bioterrorism setting as a result of an aerosol exposure. Organisms spread from the conjunctiva to regional nodes, where they cause focal necrosis and lesions.[2-4]

After an incubation period of 3-5 (range 1-14) days, oculoglandular tularemia presents as a painful "red eye" with purulent exudation, chemosis, vasculitis, and painful regional lymphadenopathy. Additional signs and symptoms may include photophobia, lacrimation, itching, local edema, and changes in visual acuity. There is a potential for lymph node suppuration, hematogenous dissemination, and development of sepsis.[2-4]

Laboratory values are generally nonspecific, and Gram stain of conjunctival scrapings may or may not demonstrate organisms.[2]

Oropharyngeal Tularemia

Oropharyngeal or gastrointestinal tularemia occurs via ingestion of contaminated food including undercooked meat, contaminated water or droplets, and oral inoculation from the hands after contact with contaminated material.[3, 4]

After an incubation period of 3-5 (range 1-14) days, oropharyngeal tularemia presents either as acute pharyngitis with cervical lymphadenopathy or as ulcerative gastrointestinal lesions with fever, abdominal pain, diarrhea, nausea, vomiting, mesenteric lymphadenopathy, and gastrointestinal bleeding. Severity can range from mild diarrhea to overwhelming ulceration with frank gastrointestinal bleeding and sepsis. A large inoculum (approximately 10^8 organisms) is required to transmit disease orally. There is a potential for lymph node suppuration, hematogenous dissemination, and development of sepsis.[2-4] Routine tests are generally nonspecific. Leukocytosis may or may not be present.[2]

Typhoidal Tularemia

Typhoidal (septicemic) tularemia is an acute, nonspecific febrile illness associated with *F. tularensis* without prominent lymphadenopathy.

TYPHOIDAL TULAREMIA	
Incubation Period	3-5 days (range 1-14 days)
Transmission	• Site of primary infection usually unknown
Signs and Symptoms	• Fever, chills, headache, malaise, weakness, myalgias, arthralgias, cough • Prostration, dehydration, hypotension, pharyngitis • Watery diarrhea, anorexia, nausea, vomiting, abdominal pain (children may have more severe GI involvement) • Generalized maculopapular rash with progression to pustules or erythema-nodosum type rash may occur • Splenomegaly and hepatomegaly (not common)
Progression and Complications	• Secondary pneumonia • Hematogenous spread to other organs – osteomyelitis, pericarditis, peritonitis, endocarditis, meningitis • Sepsis • Rhabdomyolysis • Cholestasis with jaundice • Renal failure • Debilitating illness lasting several months
Laboratory Findings	• Pleural effusions • Leukocytosis; differential may be normal • Liver enzymes and/or CK may be abnormal • Sterile pyuria may occur
CK, creatine kinase; GI, gastrointestinal.	

DIFFERENTIAL DIAGNOSIS

A high index of suspicion is required to diagnose tularemia because there are no readily available rapid and specific confirmatory tests. In addition, the various forms of tularemia can have a nonspecific appearance and/or resemble a wide range of much more common illnesses.

Differential: Pneumonic Tularemia

The following are clinical syndromes that can appear similar to the pneumonic form of tularemia:

- bacterial pneumonia (*Mycoplasma, Staphylococcus, Streptococcus, Haemophilus, Klebsiella, Moraxella Legionella)*
- *Chlamydia* infection
- Q fever
- tuberculosis
- inhalational anthrax
- pneumonic plague
- fungal pulmonary disease (histoplasmosis, coccidiodomycosis)
- Viral pneumonia (influenza, hantavirus, RSV, CMV)
- severe acute respiratory syndrome (SARS)
- other causes of atypical or chronic pneumonias

Differential: Glandular and Ulceroglandular Tularemia

The following are clinical syndromes that can appear similar to the glandular and ulceroglandular forms of tularemia:

- pyogenic bacterial infections
- cat-scratch disease (Bartonella)
- syphilis
- chancroid
- lymphogranuloma venereum
- tuberculosis
- nontuberculosis mycobacterial infection
- toxoplasmosis
- sporotrichosis
- rat-bite fever
- anthrax
- plague
- herpes simplex virus infection
- adenitis or cellulitis (*Staphylococcus* or *Streptococcus*)
- *Pasteurella* infections
- rickettsial infections
- orf virus infection

Differential: Oculoglandular Tularemia

The following are clinical entities that can appear similar to the oculoglandular form of tularemia:

- pyogenic bacterial infections
- adenoviral infection
- syphilis
- cat-scratch disease
- herpes simplex virus infection
- varicella-Zoster virus infection
- sporotrichosis
- coccidioidomycosis
- tuberculosis

Differential: Oropharyngeal Tularemia

The following are causes of syndromes that appear similar to the oropharyngeal form of tularemia:

- *Streptococcus* pharyngitis
- infectious mononucleosis
- adenoviral infection
- diphtheria
- GI anthrax

Differential: Typhoidal Tularemia

The following are causes of syndromes that can appear similar to typhoidal forms of tularemia:

- *Salmonella* spp. infection
- brucellosis
- endocarditis
- leptospirosis

- *Legionella* infection
- *Chlamydia* infection
- Q fever
- disseminated mycobacterial or fungal infection
- rickettsial infections
- malaria
- meningococcemia
- septicemic plague
- septicemia caused by other gram-negative bacteria
- *Staphylococcus* or *Streptococcus* toxic shock syndrome
- other causes of prolonged fever without localizing signs

LABORATORY DIAGNOSIS

The diagnosis of tularemia requires a high index of suspicion because the disease often presents with nonspecific symptoms and nonspecific results of routine lab tests.

If you are testing or considering testing for tularemia, you should:

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830).** SFDPH can authorize and facilitate testing, and will initiate the public health response as needed.
- **Inform your lab that tularemia is under suspicion. *F. tularensis* may pose a risk to lab personnel.**

Although recommended, microscopy and culture are difficult and often not fruitful. The organism is rarely seen on stained clinical specimens and is difficult to isolate using routine culture media and conditions. However, isolation is possible from a variety of clinical specimens if culture conditions are optimized. Even still, some strains may require up to a week to develop visible colonies, especially if the patient has been placed on bacteriostatic antibiotic therapy. Because of the need for nonroutine laboratory methods and because *F. tularensis* is a risk to laboratory personnel, clinicians should notify the laboratory when tularemia is suspected. [3, 21]

Diagnosis is most commonly confirmed by serologic testing. Antibody detection assays include tube agglutination, microagglutination, hemoagglutination, and enzyme-linked immunosorbent assay (ELISA). Significant antibodies appear around the end of the 2nd week of illness, peak at 4-5 weeks, and can persist indefinitely. A single titer of 1:160 or greater (by tube agglutination) or 1:128 or greater (by microagglutination) is a presumptive positive; a four-fold rise in titer is required for definitive serologic diagnosis.[3, 21]

Although rapid diagnostic tests are not widely available, the public health laboratory system may be able to provide timely testing of certain clinical specimens (e.g., polymerase chain reaction (PCR) testing).

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfcdcp.org).

Treatment

First-line treatment for tularemia is streptomycin or gentamicin.[2, 20, 22, 23] Flouroquinolone antibiotics have also been effective[24, 25]. Other alternatives are tetracyclines and chloramphenicol. However these drugs are bacteriostatic and their uses have produced more relapses than treatment with aminoglycosides.[20, 26] Clinicians should be aware that *F. tularensis* strains released intentionally may be resistant to antimicrobials.[3]

Supportive care, including fluid management and hemodynamic monitoring, should be considered in all patients. Intensive care with respiratory support may be necessary in patients with complications.[2]

Contained casualty setting: The Working Group recommends parenteral antimicrobial therapy when individual medical management is available **(Table 1)**. Therapy may be switched to oral antimicrobials when clinically indicated.[3]

Mass casualty setting: Use of oral antibiotics may be necessary if the number of patients exceeds the medical care capacity for individual medical management **(Table 2)**.[3]

TABLE 1. TREATMENT OF TULAREMIA IN THE CONTAINED CASUALTY SETTING[3]

Patient Category	Therapy Recommendation*
Adults: **Preferred Choices**	Streptomycin, 1 gm IM BID for 10 days‡†§ ***OR*** Gentamicin, 5 mg/kg IM or IV QD for 10 days‡†
Adults: **Alternative Choices**	Doxycycline, 100 mg IV BID for 14-21 days† ***OR*** Chloramphenicol, 15 mg/kg IV QID for 14-21 days** ***OR*** Ciprofloxacin, 400 mg IV BID for 10 days†
Children: **Preferred Choices**	Streptomycin, 15 mg/kg IM BID (max 2 gm/day) for 10 days‡ ***OR*** Gentamicin, 2.5 mg/kg IM or IV TID for 10 days‡
Children: **Alternative Choices**	Doxycycline, >45 kg, give adult dosage for 14-21 days <45 kg, give 2.2 mg/kg IV BID for 14-21 days ***OR*** Chloramphenicol, 15 mg/kg IV QID for 14-21 days** ***OR*** Ciprofloxacin, 15 mg/kg IV BID (max 1 gm/day) for 10 days

* These treatment recommendations reflect those of the Working Group on Civilian Biodefense and may not necessarily be approved by the Food and Drug Administration.

† Acceptable for pregnant women.

§ Streptomycin is not as acceptable as gentamicin for use in pregnant women because irreversible deafness in children exposed in utero has been reported with streptomycin use.

‡ Aminoglycosides must be adjusted according to renal function.

** Concentration should be maintained between 5 and 20 µg/mL; concentrations >25 µg/mL can cause reversible bone marrow suppression.

TABLE 2. TREATMENT OF TULAREMIA IN THE MASS CASUALTY SETTING AND FOR POSTEXPOSURE PROPHYLAXIS*[3]

Patient Category	Therapy Recommendation*
Adults (Including Pregnant Women)	Doxycycline, 100 mg PO BID for 14 days‡ ***OR*** Ciprofloxacin, 500 mg PO BID for 14 day‡
Children	Doxycycline, >45 kg, give adult dosage for 14 days <45 kg, give 2.2 mg/kg PO BID for 14 days ***OR*** Ciprofloxacin, 15 mg/kg PO BID (max 1 gm/day) for 10 days

* These treatment recommendations reflect those of the Working Group on Civilian Biodefense and may not necessarily be approved by the Food and Drug Administration.

‡ Although fetal toxicity may occur with doxycycline use, the Working Group recommended doxycycline or ciprofloxacin for postexposure prophylaxis of pregnant women or for treatment of infection of pregnant women in the mass casualty setting.

Postexposure Prophylaxis

Antibiotic prophylaxis should begin as soon as possible and preferably within 24 hours after exposure to an infectious aerosol containing *F. tularensis* **(Table 2)**. Postexposure prophylactic antibiotic treatment of close contacts of tularemia patients is not recommended because human to human transmission of *F. tularensis* is not known to occur.[3]

Vaccination

A live, attenuated vaccine was developed and has been used in the United States to protect laboratory personnel who work with *F. tularensis*. This vaccine is currently under review by the Food and Drug Administration and is unavailable.[3] Clinical trials to develop a new tularemia vaccine are underway but it is not likely that a vaccine will be widely available in the near future.

COMPLICATIONS AND ADMISSION CRITERIA

Disease manifestations and complications are typically related to the portal of entry of *F. tularensis*. Pneumonic tularemia may result in severe pneumonia, lung abscess, or acute respiratory distress syndrome (ARDS). Glandular and ulceroglandular tularemia may progress to lymph node suppuration and secondary pneumonia. Oculoglandular tularemia can cause localized lymph node suppuration, whereas oropharyngeal tularemia has been associated with mesenteric lymphadenitis, gastrointestinal (GI) ulceration, and GI bleeding. Typhoidal tularemia not uncommonly progresses to secondary pneumonia. All forms of human tularemia carry the potential for hematogenous dissemination of the organism to other organs such as bone, pericardium, and peritoneum, and for progression to sepsis and multiorgan failure.[2-4]

Admission to the hospital is generally advisable for patients with any form of tularemia, in order to administer antibiotics intravenously and to monitor for disease progression.

INFECTION CONTROL

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfcdcp.org).

Clinicians should notify local public health authorities, their institution's infection control professional, and their laboratory of any suspected tularemia cases. Public health authorities may conduct epidemiologic investigations and implement disease control interventions to protect the public. Both the Hospital Infection Control Practices Advisory Committee (HICPAC) of the CDC and the Working Group for Civilian Biodefense recommend **Standard Precautions** for patients with tularemia in a hospital setting without the need for isolation. Routine laboratory procedures should be carried out under Biosafety Level 2 (BSL-2) conditions; however, manipulation of cultures or other activities that may produce aerosol or droplets (e.g., centrifuging, grinding, vigorous shaking) require BSL-3 conditions.[3]

Decontamination

Contaminated surfaces can be disinfected with commercially available bleach or a 1:10 dilution of household bleach and water. All persons exposed to an aerosol containing *F. tularensis* should be instructed to wash body surfaces and clothing with soap and water.[3].

PEARLS AND PITFALLS

1. The onset of tularemia is usually abrupt, with fever, headache, chills and rigors, generalized body aches, and coryza. A pulse-temperature dissociation has been noted in as many as 42% of patients.[3]
2. Clinicians should familiarize themselves with the local epidemiology of tularemia. The occurrence of human cases may follow a local tularemia epizootic (outbreak of disease in an animal population). Occurrence of pneumonic tularemia in a low-incidence area should prompt consideration of bioterrorism.[3]
3. The diagnosis of tularemia relies heavily on clinical suspicion. Routine laboratory tests are usually nonspecific. The organism is usually not apparent on gram-stained smears or tissue biopsies and usually does not grow on standard culture plates. However, *F. tularensis* may be recovered from blood and body fluids using special supportive media. Because of this and its potential hazards to laboratory personnel, the laboratory should be notified if tularemia is suspected.

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VIRAL HEMORRHAGIC FEVER

JULY 2008

Outline

Immediately report any suspected or confirmed cases of viral hemorrhagic fevers to:

SFDPH Communicable Disease Control
(24/7 Tel: 415-554-2830)

- By law, health care providers must report suspected or confirmed cases of viral hemorrhagic fever to their local health department immediately [within 1 hr].
- SFDPH Communicable Disease Control can facilitate specialized testing and will initiate the public health response as needed.

Also notify your:

- Infection Control Professional

Clinical Laboratory

INTRODUCTION

Viral hemorrhagic fevers (VHFs) refer to a group of illnesses caused by several families of viruses, including:

- **Filoviridae** (Ebola and Marburg viruses)
- **Arenaviridae** (Lassa fever and New World hemorrhagic fever)
- **Bunyaviridae** (Rift Valley fever, Crimean-Congo fever, and "agents of hemorrhagic fever with renal syndrome")
- **Flaviviridae** (yellow fever, Omsk hemorrhagic fever, Kyasanur Forest disease, and dengue)

Many VHF viruses are virulent, and some are highly infectious (e.g., filoviruses and arenaviruses) with person-to-person transmission from direct contact with infected blood and bodily secretions. Effective therapies and prophylaxis are extremely limited for VHF; therefore, early detection and strict adherence to infection control measures are essential.

The Working Group for Civilian Biodefense considers some hemorrhagic fever viruses to pose a more serious threat as potential biological weapons based on risk of morbidity and mortality, feasibility of production, and ability to cause infection through aerosol dissemination. These include Ebola, Marburg, Lassa fever, New World arenaviruses, Rift Valley fever, yellow fever, Omsk hemorrhagic fever, and Kyasanur Forest disease.[1] Therefore, this chapter will focus only on these VHF viruses and will not include a discussion of dengue fevers, hemorrhagic fever with renal syndrome (e.g., hantavirus), and Crimean-Congo hemorrhagic fevers.

EPIDEMIOLOGY

VHF viruses as Biological Weapons

Of the potential ways in which VHFs could be used as a biological weapon, an aerosol release is expected to have the most severe medical and public health outcomes.

An intentional release of a VHF virus would have the following characteristics:[2]

- Multiple similarly presenting cases clustering in time:
    - acute nonspecific febrile illness with onset 2 to 21 days after the initial release (may include fever, myalgias, rash, and encephalitis)
    - severe illness with a fever and hemorrhagic manifestations
- Atypical host characteristics: unexpected, unexplained cases of acute illness in previously healthy persons, or people with hemorrhagic symptoms who have no conditions predisposing for hemorrhagic illness
- Unusual geographic clustering: cases occurring in an area where naturally occurring VHF is not endemic
- Absence of risk factors: patients lack VHF exposure risk factors (e.g., travel to a VHF endemic country such as South America, Africa, or Asia; handling animal carcasses; contact with people sick with VHF).

In the event of an intentional release, some VHFs could infect susceptible animals and potentially lead to establishment of the disease in the environment.

Naturally Occurring Viral Hemorrhagic Fever

All of the VHF agents cause sporadic disease or epidemics in areas of endemicity. The routes of transmission are variable, but most are zoonotic with spread via arthropod bites or contact with infected animals. Person-to-person spread is a major form of transmission for many of the viruses. Epidemiologic characteristics for each virus are described in the tables below.

EPIDEMIOLOGIC CHARACTERISTICS OF VHF VIRUSES				
Virus		**Worldwide Occurrence**	**Reservoir/ Vector**	**Transmission**
Filoviruses	**Ebola**	• Identified in 1976 during outbreaks in the Democratic Republic of Congo (formerly known as Zaire) and Sudan. Four species of Ebola virus are recognized and named after the region where they were discovered: Ivory Coast, Sudan, Zaire, and Reston • Reported cases of naturally occurring infections have occurred in Africa: Democratic Republic of Congo (1976, 1995), Sudan (1976, 1979, 2004), Gabon (1994, 1996, 2001-02), Ivory Coast (1994), Uganda (2000-01), Republic of Congo (2001-02, 2003-04, 2005) • Laboratory-acquired infections have occurred in England (1976) • Ebola has been introduced to quarantine facilities in United States (1989, 1990, 1996), Italy (1992), Philippines (1996)	unknown[A]/ unknown	Person-to-person transmission[B] occurs via: • Contact with blood, secretions, or tissue of infected patient[C] (sexual transmission may occur up to 3 months after clinical illness ends) • Contact with cadaver • Airborne transmission (suspected) • Parenteral inoculation (unsterilized needles, accidental needle sticks) • Contact with blood, secretions, or tissue of infected nonhuman primate • Exposure in laboratory
	Marburg	• Identified in 1967 in Germany when laboratory staff handling tissues from African green monkeys became infected • Reported cases of naturally occurring infections have occurred in: South Africa[D] (1975), Western Kenya (1987, 1980), Democratic Republic of Congo (1998-2000), Angola (2004-2005) • Laboratory-acquired infections have occurred in Germany (1967)	unknown[E]/ unknown	
Arenaviruses	**Lassa**	• Identified in 1969 in Nigeria • Lassa fever is endemic in West African countries between Nigeria and Senegal. There are an estimated 100,000-300,000 annual infections in West Africa. Nosocomial outbreaks and endemic transmission are more common during the dry season (January – April). Outbreaks have occurred in Sierra Leone, Guinea, Liberia, and Nigeria. • Lassa fever is occasionally imported to other countries through travel	multimmamate mouse/ none	• Inhalation of aerosols of rodent excreta, • Ingestion of food contaminated with rodent excreta • Contact of rodents OR rodent excreta with open skin or mucous membranes Person-to-person transmission via: • Contact with infectious blood and bodily fluids • Parenteral inoculation (unsterilized needles accidental needlesticks) • Airborne transmission (suspected) • Exposure in laboratory
	New World HF	• New World HFs (or South American HF) include Junin, Machupo, Guanarito, and Sabia • Reported cases of naturally occurring infections have occurred in South America: Argentina, Bolivia, Venezuela, Brazil • An additional New World HF, Whitewater Arroyo, was isolated from 3 cases in California	rodents (mouse, wood rat)/ none	

Bunyavirus	**Rift Valley Fever**	• Reported cases of naturally occurring infections have occurred in Sub-Saharan Africa, Egypt (1977-8, 1993), Kenya & Somalia (1997-8), Saudi Arabia (2000-01), Yemen (2000-01), Tanzania (2006)[3]	ruminants (sheep, cattle, goats, buffalo)/ mosquito	• Bite of an infected mosquito • Direct contact with infected animal tissue (ruminants) • Inhalation of aerosol from infected animal carcasses (ruminants) • Transmission by ingestion of contaminated raw animal milk (suspected) • Exposure in laboratory
Flavivirus	**Yellow Fever**	• Yellow fever is endemic in Sub-Saharan Africa and tropical regions of South America (mostly in forested regions). From 2000-2004 there were 2570 cases reported in Africa and 629 in South America.[4] • Most outbreaks occur in: - West Africa and Central Africa – in Savanna zones during the rainy season - Urban and Jungle regions of sub-Saharan Africa - South America – forested areas of Bolivia, Brazil, Columbia, Ecuador, Peru, Venezuela, French Guiana, Guyana	primate/ *Aedes* and *Haemagogus* mosquitoes	• Bite of an infected mosquito • Exposure in laboratory
	Kyasanur Forest disease virus	• First identified in 1957 from a sick monkey from the Kyasanur forest in the Karnataka State, India. Recently, a similar virus was discovered in Saudi Arabia. • Kyasanur Forest disease is only found in the Karnataka State in India, where 400-500 cases are reported annually.[5]	Vertebrates[F]/ Tick[G]	• Bite of an infected tick; • Inhalation of aerosols by laboratory workers during cultivation of these viruses
	Omsk HF	• Omsk HF (OHF) was first identified in 1947 in Omsk, Russia. Epizootics began occurring in western Siberia among newly introduced muskrats (for fur trade) and caused large outbreaks in humans from 1945-1958.[6] • Cases of Omsk HF have been reported in central Asia (western Siberian regions of Omsk, Novosibirsk, Kurgan, Tyumen). From 1988-1997, there were 165 cases of Omsk reported from these regions.[7, 8] Naturally occurring infections peak in spring/early summer and autumn.[6] Few cases have occurred in recent years.[9]	rodents (vole, muskrat) – possibly water-borne/tick	• Bite of an infected tick • Contact with blood, secretions, or tissue of an infected animal • Inhalation of aerosols by laboratory workers during cultivation of these viruses • Ingestion of contaminated raw goat milk • Waterborne (suspected) • Airborne (suspected)

[A] Fruit bats are currently a candidate reservoir. Asymptomatic infections occur in bats within the geographical range of human Ebola outbreaks. [10]

[B] The initial transmission of Marburg and Ebola viruses from animals to humans is not understood.

[C] Risk of transmission is greatest during the latter stages of illness when viral loads are highest, while transmission rarely (if ever) occurs before the onset of symptoms.

[D] Case most likely exposed in Zimbabwe, traveling nurse also became infected.

[E] Fruit bats are currently a candidate reservoir. Serological evidence of infections has been noted in fruit bats in the areas of human Marburg cases.[11]

[F] Not well understood – vertebrate hosts include: rodents, bats, small mammals, monkeys

[G] Not well understood

OCCURRENCE OF VHF VIRUSES IN THE UNITED STATES	
Virus	**United States Occurrence**
Ebola	Ebola-Reston virus has been introduced into quarantine by monkeys imported from the Philippines on three occasions. In two of the three incidents (1989, 1990), four humans were infected with Ebola-Reston but did not become ill (developed antibodies).
Marburg	NA
Lassa Fever	Lassa fever is rarely encountered in the United States. In 2004, a case of imported Lassa fever occurred in a New Jersey resident who became infected while traveling in West Africa. None of the contacts of the patient developed any symptoms compatible with Lassa fever within the incubation period. This was the first reported case of Lassa fever imported into the United States since 1989.[12]
New World HF	Three cases of Whitewater Arroyo virus were reported in California in 1999-2000; all were fatal. Whitewater Arroyo has been isolated from woodrats in North America, but these were the first reported cases of human disease.
Rift Valley virus	NA
Yellow Fever	Virus spread from West Africa to United States through slave trade vessels, caused significant outbreaks, including: • Philadelphia (1793) – 10% of population died • Mississippi (1878) – 100,000 cases Yellow fever has been imported into the United States by non-immunized travelers to yellow-fever endemic countries 3 times since 1924: • 1996 (Brazil to Tennessee)[13] • 1999 (Venezuela to Marin County, CA)[4] • 2002 (Brazil to Texas)[14] All cases were fatal
Kyasanur Forest disease virus	NA
Omsk HF	NA

CLINICAL FEATURES

The clinical features of VHF vary according to the virus and are detailed by disease below. However, in the case of bioterrorism, the virus may not initially be known; therefore, clinical features of VHFs, in general, are also provided.

CLINICAL FEATURES OF VIRAL HEMORRHAGIC FEVER[A]	
Early Signs	• High fever, headache, malaise, fatigue, arthralgias/ myalgias, prostration, nausea, abdominal pain, nonbloody diarrhea • Mild hypotension, relative bradycardia, tachypnea, conjunctival involvement , pharyngitis, rash or flushing
Progression (1-2 weeks)	• Hemorrhagic manifestations (e.g., petechiae, hemorrhagic or purpuric rash, epistaxis, hematemesis, melena, hemoptysis, hematochezia, hematuria) • CNS dysfunction (e.g., delirium, convulsions, cerebellar signs, coma) • Hepatic involvement (e.g., jaundice, hepatitis)
Complications and Sequelae	• Shock, DIC, multi-system organ failure • Illness-induced abortion in pregnant women • Transverse myelitis • Uveitis • Pericarditis • Orchitis

	• Parotitis • Pancreatitis • Hearing or vision loss • Impaired motor coordination • Convalescence may be prolonged or complicated by weakness, fatigue, anorexia, cachexia, alopecia, arthralgias
Laboratory Findings	• Leukopenia (except in Lassa) • Leukocytosis • Thrombocytopenia • Elevated liver enzymes • Anemia or hemoconcentration • Coagulation abnormalities (e.g., prolonged bleeding time, prothrombin time, and activated partial thromboplastin time, elevated fibrin degradation products, and increased fibrinogen) • Proteinuria, hematuria, oliguria, and azotemia
[A] Adapted from [1] CNS, central nervous system; DIC, disseminated intravascular coagulation.	

Ebola / Marburg:

Case-fatality of Ebola ranges from 50% to 90% and that for Marburg, from 23% to 70%.

Considerations for pregnant women: High mortality from Ebola infection in pregnant women (95.5%), as well as high rates of fetal and neonatal loss (100%) have been reported. [15]

CLINICAL FEATURES OF EBOLA/MARBURG		
Incubation Period	Prominent Clinical Features	Laboratory Findings
2-21 days	• Acute onset of fever, myalgias/arthralgias, headache, prostration, fatigue (< 1 week) • Nausea, vomiting, abdominal pain, diarrhea, chest pain, cough, pharyngitis, hiccups • Maculopapar rash (day 5 after symptom onset) • Hemorrhagic manifestations • Photophobia, conjunctival inflammation, lymphadenopathy, hepatitis, pancreatitis (common) • CNS dysfunction • Shock with DIC and organ failure (week 2 after symptom onset) • Complications and sequelae: arthralgias, ocular disease, parotitis, orchitis, hearing loss, pericarditis, transverse myelitis	• Leukopenia (early) • Leukocytosis (late) • Thrombocytopenia (early) • Elevated liver enzymes • Elevated amylase • Lab features of DIC

Lassa Fever

Most people infected with Lassa fever have a mild or subclinical presentation (80%). Severe disease occurs in 12-20%, with overall case-fatality around 1% (10-25% mortality in hospitalized patients). During an outbreak, a clinical combination of fever, pharyngitis, retrosternal pain, and proteinuria was predictive of laboratory-confirmed disease in 70% of cases. Findings associated

with death include hypotension, peripheral vasoconstriction, oliguria, edema, pleural effusions, and ascites. Lassa fever requires a high index of suspicion because clinical features are nonspecific and vary from patient to patient. Recovery generally begins around day 10 but may be accompanied by prolonged weakness and fatigue.[16]

Considerations for children: Clinical features of Lassa fever infection in children may be even more difficult to diagnose due because of heterogeneous presentation. One syndrome in children less than 2 years old is marked by severe generalized edema, abdominal distension, and bleeding manifestations (this is associated with high case fatality of 75%.[16])

Considerations for pregnant women: Case-fatality in pregnant women is higher than in nonpregnant women, and risk of death increases in the third trimester (30%). Evacuation of uterus (i.e., delivery, spontaneous abortion, or evacuation of retained products of conception) can significantly reduce risk of death in the pregnant woman. Lassa virus infection leads to a high rate of fetal and neonatal death (>80%).[17]

CLINICAL FEATURES OF LASSA FEVER[A]

Incubation Period	Prominent Clinical Features	Laboratory Findings
3-16	• Gradual onset of fever, weakness, pain, arthralgias • Chest and back pain, exudative pharyngitis, cough, abdominal pain, vomiting (very common) • Diarrhea and proteinuria (common) • Facial and pulmonary edema, mucosal bleeding, pleural effusions, neurological involvement (encephalopathy, coma, seizures), ascites, shock (less common) • Illness-induced abortion among pregnant women Complications & Sequelae: 8th cranial nerve damage with hearing loss, pericarditis	• Leukocyte & platelet counts often normal • Elevated liver enzymes may occur

[A] Adapted from [1, 2, 6]

New World Hemorrhagic Fevers

The New World hemorrhagic fevers (Junin, Machupo, Guanarito, Sabia) have similar clinical features and progression. Mortality ranges from 15% to 30% and recovery generally takes 2-3 weeks. Sequelae are not common.[6]

Considerations for pregnant women: Case-fatality from New World Hemorrhagic Fever infection in pregnant women is higher than non-pregnant women. Infection also leads to a high rate of fetal death.[6]

CLINICAL FEATURES OF NEW WORLD HEMORRHAGIC FEVERS[A]		
Incubation Period	Prominent Clinical Features	Laboratory Findings
7-12 days (range 5-19)	• Gradual onset of fever, malaise, myalgias (especially lower back), pharyngitis • Drowsiness, dizziness, tremor, epigastric pain and/or constipation, photophobia, retro-orbital pain, conjunctivitis, lymphadenopathy, postural hypotension • Hemorrhagic manifestations (e.g., petechial rash [oral and dermal], facial flushing, facial edema, capillary leak syndrome, membrane hemorrhage, narrowing pulse pressure, vasoconstriction) • CNS dysfunction (e.g., hyporeflexia, gait abnormalities, palmomental reflex, tremors, other cerebellar signs) • Shock, coma, seizures	• Leukopenia • Thrombocytopenia • Proteinuria • Rising hematocrit
[A]Adapted from [1, 2, 6]		

Rift Valley Fever

Rift valley fever (RVF) has not been documented to spread from person to person; however, low titers of virus have been isolated from throat washings. There has been one case where vertical transmission was suspected.[18] Historically the case-fatality estimate of RVF is less than 1%; however, a recent outbreak in Saudi Arabia (2000-01) had an overall case-fatality of 14-17% (33% case fatality in patients admitted to RFV unit because of severe disease). Factors associated with high mortality include hepatorenal failure, severe anemia, hemorrhagic or neurological manifestations, jaundice and shock.[3, 19]

CLINICAL FEATURES OF RIFT VALLEY FEVER[A]		
Incubation Period	Prominent Clinical Features	Laboratory Findings
2-6 days	• Fever, nausea, vomiting • Abdominal pain, diarrhea, jaundice • CNS dysfunction • Hemorrhagic disease (1-17%) • Ocular involvement (photophobia, retro-orbital pain, retinitis, vision loss, scotoma) • Renal involvement or failure • Shock	• Thrombocytopenia • Leukopenia • Severe anemia • Elevated liver enzymes • Elevated LDH and CK
[A]Adapted from [1-3, 6, 19] CNS, central nervous system; CK, creatine kinase; LDH, lactate dehydrogenase.		

Yellow Fever

Yellow fever may resolve after a very mild course or may progress to moderate or severe illness (15%) after a short remission. Death occurs in 7-10 days after onset of illness.[2, 6]

CLINICAL FEATURES OF YELLOW FEVER[A]		
Incubation Period	Prominent Clinical Features	Laboratory Findings
3-6 days	Prodrome: • Acute onset of fever, headache, myalgias, • Facial flushing, conjunctival injection Illness may resolve, enter remission (lasts hours or days), or progress to: • High fever, headache, severe myalgias (especially back), nausea, vomiting, abdominal pain, weakness, prostration, bradycardia • Hemorrhagic manifestations • Fulminant infection with severe hepatic involvement • Shock, myocardial failure, renal failure, seizures, coma • Pneumonia, sepsis	• Leukopenia (early), • Leukocytosis (late) • Thrombocytopenia • Elevated liver enzymes and bilirubin • Albuminuria • Azotemia • Alkaline phosphatase levels only slightly elevated
[A]Adapted from:[1, 2, 6]		

Kyasanur Forest disease

Kyasanur Forest disease is characterized by biphasic illness: 50% of patients who go on to develop the second phase with meningoencephalitis. Case-fatality ranges from 3% to 10%.

CLINICAL FEATURES OF KYASANUR FOREST DISEASE		
Incubation Period	Prominent Clinical Features	Laboratory Findings
2-9 days	Phase I (6-11 days): • Acute onset of fever, myalgias, headache (6-11 days) • Conjunctival involvement, soft palate lesions, GI symptoms • Hyperemia of face and trunk (but no rash) • Lymphadenopathy • Hemorrhagic manifestations (not severe) Phase II: • Afebrile period of 9-21 days followed by meningoencephalitis (50% of patients)	• Leukopenia • Lymphopenia or lymphocytosis • Thrombocytopenia • Abnormal liver function
GI, gastrointestinal.		

Omsk Hemorrhagic fever

Omsk hemorrhagic fever (OHF) is similar to Kyasanur Forest disease. Some also characterize OHF as a biphasic illness with the first phase lasting 5-12 days with an estimated 30-50% of patients

going on to experience remission of fever, febrile illness, and more severe disease. Case fatality ranges from 0.5% to 3%. Recovery may take weeks, but sequelae are not common.[1, 7]

CLINICAL FEATURES OF OMSK HEMORRHAGIC FEVER[A]

Incubation Period	Prominent Clinical Features	Laboratory Findings
3-8 days (range 1-10 days)	• Acute onset of fever, headache, myalgias • Cough, conjunctivitis, soft pallet lesions, GI symptoms • Hyperemia of face and trunk (but no rash) • Lymphadenopathy, splenomegaly • Hemorrhagic manifestations (not severe) • Pneumonia, CNS dysfunction, meningeal signs, diffuse encephalitis	• Leukopenia • Thrombocytopenia

[A]Adapted from [2, 6, 7]

CNS, central nervous system; GI, gastrointestinal.

DIFFERENTIAL DIAGNOSIS

A high index of suspicion is required to diagnose VHF because there are no readily available rapid and specific confirmatory tests. In addition, the VHF viruses can have a nonspecific appearance or resemble a wide range of much more common illnesses.

With a VHF virus used as a biological weapon, patients are less likely to have risk factors for natural infection such as travel to VHF-endemic countries (Africa, Asia, or South America), contact with sick animals or people, or arthropod bites within 21 days of symptom onset. The observation of a severe illness with bleeding manifestations as its primary feature, which develops in several related cases should be highly suspicious for VHF.

The Working Group for Civilian Biodefense suggests considering VHF in any patient with the following clinical presentation:

- Acute onset of fever (<3 weeks duration) in severely ill patient
- Hemorrhagic manifestations (at least two of the following: hemorrhagic or purpuric rash, epistaxis, hematemesis, hemoptysis, blood in stool, or other bleeding)
- No conditions predisposing for hemorrhagic illness
- No alternative diagnosis

Differential Diagnosis–Infectious Conditions (viral, rickettsial, bacterial and parasitic) [1, 2]

- Gram-negative bacterial septicemia
- toxic shock syndrome (*Staphylococcus, Streptococcus*)
- meningococcemia
- secondary syphilis
- septicemic plague
- salmonellosis (*Salmonella typhi*)
- influenza
- measles
- rubella
- dengue hemorrhagic fever
- hemorrhagic varicella
- hemorrhagic smallpox
- Viral hepatitis

- shigellosis
- *Chlamydia* infection
- borreliosis
- leptospirosis
- rickettsiosis
- hantavirus pulmonary syndrome
- malaria
- African trypanosomiasis

Noninfectious Conditions [1, 2]

- thrombotic or idiopathic thrombocytopenic purpura
- acute leukemia
- hemolytic-uremic syndrome
- collagen-vascular diseases

LABORATORY DIAGNOSIS AND RADIOGRAPHIC FINDINGS

Viral hemorrhagic fevers are a risk to laboratory personnel. Clinicians should immediately notify their laboratory, local health department, and infection control professional when VHF is suspected. In the event of an outbreak, public health authorities will provide recommendations for specimen collection based on this situation (e.g., identification of etiologic agent, laboratory capacity).

If you are testing or considering testing for viral hemorrhagic fever, you should:

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830).**
  SFDPH can authorize and facilitate testing, and will initiate the public health response as needed.
- **Inform your lab that viral hemorrhagic fever is under suspicion.**

Diagnosis of VHF requires a high index of suspicion because the disease initially presents with nonspecific symptoms and non-specific results of routine lab tests. Routine laboratory findings for specific HF viruses are listed in the clinical features tables.

A number of test methods can be used to diagnose VHF at specialized laboratories. These include antigen-capture testing by enzyme-linked immunosorbent assay (ELISA), IgM antibody testing, paired acute-convalescent serum serologies, reverse transcriptase polymerase chain reaction (RT-PCR), immunohistochemistry methods, and electron microscopy. Viral identification in cell culture is the gold standard of viral detection; however, this may only be attempted at a Biosafety Level 4 (BSL-4) facility. Combined ELISA Ag/ IgM has high specificity and sensitivity for early diagnosis of Lassa fever and provides prognostic information (presence of indirect fluorescent antibody early in disease associated with death).[20]

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfcdcp.org).

Treatment

Medical management should follow the guidelines below:

MEDICAL MANAGEMENT RECOMMENDATIONS

Categorization	Medical Management
Exposed Persons	Medical Surveillance No post-exposure prophylaxis is recommended[A]
Suspected VHF Case of Unknown Viral Type	Supportive Care + Ribavirin Therapy[B]
Suspected or Confirmed VHF Case known to be caused by an Flavivirus or Filovirus	Supportive Care Only
Suspected Confirmed VHF Case known to be caused by an Arenavirus or Bunyavirus	Supportive Care + Ribavirin Therapy

[A] Previous CDC recommendations state that Ribavirin should be given to high-risk contacts of persons with Lassa fever. The Working Group on Civilian Biodefense recommends medical surveillance only, and notes that the CDC guidelines may be under review.
[B] Ribavirin therapy should be initiated promptly unless another diagnosis is confirmed or the etiologic agent is known to be a Flavivirus or Filovirus.

Medical Surveillance: Persons should be instructed to record their temperature twice daily and report any temperature of 38.0ºC or 100.4 ºF or higher (or any other signs or symptoms) to their clinician and/or the proper public health authorities. Patients should be advised not to share thermometers between family members and to properly disinfect thermometers after each use.

Supportive Care: Supportive care, including careful maintenance of fluid and electrolyte balance and circulatory volume is essential for patients with all types of VHF. Mechanical ventilation, dialysis, and appropriate therapy for secondary infections may be indicated. Treatment of other suspected causes of disease, such as bacterial sepsis, should not be withheld while awaiting confirmation or exclusion of the diagnosis of VHF. Anticoagulant therapies, aspirin, nonsteroidal anti-inflammatory medications, and intramuscular injections are contraindicated.

Ribavirin Therapy: Ribavirin is recommended for: (1) suspect or probable cases of *VHF of unknown viral type* or (2) suspect, probable, or confirmed cases *caused by an Arenavirus or Bunyavirus*. Ribavirin has shown in vitro and in vivo activity against Arenaviruses (Lassa fever, New World hemorrhagic fevers) and Bunyaviruses (Rift Valley fever and others). Ribavirin has shown no activity against, and is not recommended for Filoviruses (Ebola and Marburg hemorrhagic fever) or Flaviviruses (Yellow fever, Kyasanur Forest disease, Omsk hemorrhagic fever). Recommendations for intravenous (IV) ribavirin therapy are shown below. Use of oral ribavirin may be necessary if the number of patients exceeds the medical care capacity for individual medical management.

RIBAVIRIN THERAPY FOR PATIENTS WITH VHF OF UNKNOWN CAUSE OR CAUSED BY AN ARENAVIRUS OR BUNYAVIRUS[A]		
	IV Therapy in Contained Casualty Situation[B]	**Therapy in a Mass-Casualty Setting[B]**
Adult	**Ribavirin,** • Loading dose 30 mg/kg (max 2 gm) IV, Followed by: • 16 mg/kg (max 1 gm) IV q6 hr for 4 days, Followed by: • 8 mg/kg (max 500 mg) IV q8 hr for 6 days	**Ribavirin,** • Loading dose of 2000 mg PO, Followed by: • (Weight >75 kg): 1200 mg/day PO in 2 divided doses (600 mg in am and 600 mg in pm) for 10 days[C] • (Weight <75 kg): 1000 mg/day PO in divided doses (400 mg in am and 600 mg in pm) for 10 day[C]
Children[D]	Same as for adults	• Loading dose of 30 mg/kg PO, Followed by: • 15 mg/kg/d PO in 2 divided doses for 10 days
Pregnant women[E]	Same as for non-pregnant adults	Same as for non-pregnant adults

[A] Ribavirin is not labeled for use in treatment of VHF by the US Food and Drug Administration (FDA) for treatment and must be used under an Investigational New Drug (IND) protocol.
[B] Use of oral vs. parenteral treatment will depend on resource availability
[C] The current available formulation of ribavirin is 200-mg capsules, which cannot be broken open.
[D] IV and oral ribavirin are not approved for children by the FDA; however, the benefits may outweigh the risk of ribavirin therapy.
[E] Ribavirin is contraindicated in pregnant women; however, the benefits may outweigh the fetal risk of ribavirin therapy.

Passive immunotherapy with convalescent human plasma has been used in the treatment and prophylaxis of several VHFs with inconclusive results. Some suggest passive immunotherapy for treatment of New World HFs based on effectiveness in Argentine HF (Junin).[1, 16, 21, 22]

Post Exposure Prophylaxis

According to the Working Group on Civilian Biodefense, exposure is defined as proximity to an initial release of VHF virus, or close or high-risk contact with a patient suspected of having VHF. *High risk* contacts are defined as persons who "have had mucous membrane contact with a patient (such as during kissing or sexual intercourse) or have had percutaneous injury involving contact with a patient's secretions, excretions, or blood." *Close contact* is defined as, "those who live with, shake hands with, hug, process laboratory specimens from, or care for a patient with VHF prior to initiation of appropriate precautions."[1] Medical surveillance (see above) is recommended for 21 days following the potential exposure or contact with the ill person.

Previous recommendations from the Centers for Disease Control and Prevention (CDC)[23] state that prophylaxis with ribavirin should be given to persons exposed to Lassa virus. However, because the efficacy of ribavirin prophylaxis for Lassa virus is unknown, the Working Group also recommends that persons exposed be placed under medical surveillance until 21 days after the last exposure.[1] The CDC recommendation is under review.

Vaccine

A licensed vaccine against yellow fever is effective if given prior to exposure. It is used for travelers going to endemic areas. This vaccine does not prompt development of antibodies rapidly enough to be used in the post-exposure setting. A rare, but serious adverse reaction to yellow fever vaccine, viscerotropic and neurotropic disease, has recently been recognized and reported. [24]

There is no licensed vaccine for any of the other VHFs, though research is underway on several candidates.

Developmental VHF Therapeutics

Additional therapeutic candidates for vaccine, treatment, and prophylaxis of VHFs are currently under development.

DEVELOPMENTAL VHF THERAPEUTICS	
Virus	Candidates for vaccine, treatment, and prophylaxis
Ebola / Marburg	• A live attenuated recombinant vaccine for Ebola and Marburg HF has produced protective immune responses in non-human primates • A vaccine used as a PEP produced some protective effect for Ebola in non-human primates when administered soon after infection (20-30 min)[25] • A Phase I clinical trial for an Ebola DNA vaccine was safe and produced an immune response in humans • Treatment with small interfering RNAs (siRNAs) produced protective immune response in an animal model (guinea pigs)[26]
Lassa Fever	• An attenuated recombinant vaccine produced protective immune responses in non-human primates[27]
New World HF	• Live-attenuated vaccine available as investigational new drug in Argentine HF[28] • Passive immunotherapy with convalescent human serum has been effective in Argentine HF[16]
Rift Valley virus	• Vaccine available as investigational new drug[29]
Yellow Fever	• Licensed vaccine available (see above)
Kyasanur Forest disease virus	• Formalin inactivated vaccine licensed and used in endemic areas[30]
Omsk HF	• NA

COMPLICATIONS AND ADMISSION CRITERIA

Patients with filovirus infection (Ebola and Marburg viruses) often experience hemorrhagic and severe central nervous system (CNS) manifestations along with fever and jaundice during the first week of illness. In the second week patients defervesce and either improve markedly or die as a result of multiorgan dysfunction, shock, and disseminated intravascular coagulation. Survivors may develop one or more complications including arthralgia, orchitis, hepatitis, transverse myelitis, or uveitis.

Death from Lassa virus infection, when it occurs, is typically during the second week of illness and is associated with hypotension, edema, and capillary leak syndrome. Up to one-third of Lassa

fever survivors develop sensorineural deafness. The arenaviruses (Lassa and New World viruses) share a propensity to cause fetal demise and high mortality rates in pregnant women.

Among the bunyavirus infections (Rift Valley fever and Crimean-Congo hemorrhagic fever), a fulminant, fatal form of the disease with hemorrhage, hepatitis, and organ failure occurs in a minority of patients. Rift Valley fever encephalitis is known to occur in a small percentage of those affected.

Although many infections with yellow fever are clinically inapparent, patients may develop multisystem illness dominated by an icteric hepatitis and a severe bleeding diathesis. In the latter stages of illness encephalopathy, shock, and death may ensue. Patients who recover frequently suffer from secondary bacterial infections.

The need for hospitalization and life support will be apparent in patients with bleeding diatheses, CNS dysfunction, shock, or severe hepatorenal dysfunction. Patients exhibiting milder manifestations of VHF or who appear to be in the early stages of disease could benefit from hospitalization for supportive care and close observation. Treatment with intravenous ribavirin should be initiated in patients known to have arenavirus or bunyavirus infection and in those with VHF of unknown etiology pending viral identification.

INFECTION CONTROL

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfcdcp.org).

Clinicians should notify local public health authorities, their institution's infection control professional, and their laboratory of any suspected VHF cases. Public health authorities may conduct epidemiologic investigations and implement disease control interventions to protect the public.

Many VHF viruses are virulent, and some are highly infectious (e.g., filoviruses and arenaviruses) with *person to person transmission* from direct contact with infected blood and bodily secretions. Effective therapies and prophylaxis are extremely limited for VHF; therefore, early detection and strict adherence with infection control measures are essential. Transmission rarely (if ever) occurs before the onset of symptoms. Risk of transmission is greatest during the latter stages of illness when viral loads are highest.

Among household contacts, secondary transmission for Ebola and Marburg ranges from 10 to 20%. In the 1995 Ebola outbreak in the Democratic Republic of Congo, transmission did not occur among household contacts with no direct physical contact with patients. Persons with physical contact

with patients were at increased risk of transmission, and those with body fluid contact had the greatest risk.[31, 32]

Guidance on infection control precautions have been published by both the CDC and the Working Group for Civilian Biodefense in 2005 and 2002 respectively; these contained some inconsistencies.[1, 33] More recent guidance was provided by the CDC's Healthcare Infection Control Practices Advisory Committee.[34]

For patients infected or suspected to be infected with VHF healthcare workers and visitors should use Standard, Contact and Droplet Precautions with eye protection. Single gloves are adequate for routine patient care; double-gloving is advised during invasive procedures (e.g., surgery) that pose an increased risk for blood exposure. Routine eye protection (i.e. goggles or face shield) is particularly important. Fluid-resistant gowns should be worn for all patient contact. Airborne Precautions are not required for routine patient care; however, use of airborne infection isolation room (AIIR) is prudent when procedures that could generate infectious aerosols are performed (e.g., endotracheal intubation, bronchoscopy, suctioning, autopsy procedures involving oscillating saws). N95 or higher level respirators may provide added protection for individuals in a room during aerosol-generating procedures. When a patient with a syndrome consistent with hemorrhagic fever also has a history of travel to an endemic area, precautions are initiated upon presentation and then modified as more information is obtained. Patients with hemorrhagic fever syndrome in the setting of a suspected bioweapon attack should be managed using Airborne Precautions, including AIIRs, since the epidemiology of a potentially weaponized hemorrhagic fever virus is unpredictable.[34]

All persons exposed to VHF should immediately wash the affected skin surfaces with soap and water. Mucous membranes should be irrigated with copious amounts of water or eyewash solution. Exposed persons should receive medical evaluation and monitoring.

PEARLS AND PITFALLS

1. Since effective postexposure prophylaxis is unavailable for VHF, strict adherence to infection control measures is essential for limiting the spread of disease.
2. The risk for person-to-person transmission of VHF is highest during the latter phases of illness, when viral loads are high and disease manifestations are most severe.
3. VHF viruses are not endemic in the United States, with the rare exception of Whitewater Arroyo virus which caused three cases of human disease in California in 1999-2000 and may have been related to wild rodents. Nearly all U.S. cases of VHF have been acquired by overseas travelers or by scientific research personnel.

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INFECTION CONTROL PRECAUTIONS

Outline

STANDARD PRECAUTIONS

Use Standard Precautions, or the equivalent, for the care of all patients.

Standard Precautions apply to 1) blood; 2) all body fluids, secretions, and excretions except sweat, regardless of whether or not they contain visible blood; 3) nonintact skin; and 4) mucous membranes. Standard Precautions are designed to reduce the risk of transmission of microorganisms from both recognized and unrecognized sources of infection in hospitals.

Hand Hygiene

When hands are visibly dirty or visibly soiled with blood or other body fluids:

- Wash with either antimicrobial or non-antimicrobial soap & water

If hands are not visibly soiled:

- Use an alcohol-based hand rub or wash with an antimicrobial soap & water to decontaminate hands

Decontaminate hands before:

- Having direct contact with patients
- Donning sterile gloves before sterile procedures
- Moving from a contaminated-body site to a clean-body site during patient care
- Eating

Decontaminate hands after:

- Contact with a patient's intact skin
- Contact with body fluids or excretions, mucous membranes, nonintact skin, and wound dressings, inanimate objects (including medical equipment) in the immediate vicinity of the patient
- Removing gloves
- Using a restroom

Before eating and after using a restroom:

- Wash with either antimicrobial or non-antimicrobial soap & water

If exposure to *Bacillus anthracis* is suspected or confirmed:

- Wash with either antimicrobial or non-antimicrobial soap & water. The physical action of washing and rinsing hands under such circumstances is recommended because alcohols, chlorhexidine, iodophors, and other antiseptic agents have poor activity against spores.

Gloves

Wear gloves (clean, nonsterile gloves are adequate) when touching blood, body fluids, secretions, excretions, and contaminated items. Put on clean gloves just before touching mucous membranes and nonintact skin.

Change gloves between tasks and procedures on the same patient after contact with material that may contain a high concentration of microorganisms. Remove gloves promptly after use, before touching noncontaminated items and surfaces, and before going to another patient, and wash hands immediately to avoid transfer of microorganisms to other patients or environments.

Mask, Eye Protection, Face Shield

Wear a mask and eye protection or a face shield to protect mucous membranes of the eyes, nose, and mouth during procedures and patient-care activities that are likely to generate splashes or sprays of blood, body fluids, secretions, and excretions.

Gown

Wear a gown (a clean, nonsterile gown is adequate) to protect skin and to prevent soiling of clothing during procedures and patient-care activities that are likely to generate splashes or sprays of blood, body fluids, secretions, or excretions. Select a gown that is appropriate for the activity and amount of fluid likely to be encountered. Remove a soiled gown as promptly as possible and wash hands to avoid transfer of microorganisms to other patients or environments.

Patient-Care Equipment

Handle used patient-care equipment soiled with blood, body fluids, secretions, and excretions in a manner that prevents skin and mucous membrane exposures, contamination of clothing, and transfer of microorganisms to other patients and environments. Ensure that reusable equipment is not used for the care of another patient until it has been cleaned and reprocessed appropriately. Ensure that single-use items are discarded properly.

Environmental Control

Ensure that the hospital has adequate procedures for the routine care, cleaning, and disinfection of environmental surfaces, beds, bedrails, bedside equipment, and other frequently touched surfaces, and ensure that these procedures are being followed.

Linen

Handle, transport, and process used linen soiled with blood, body fluids, secretions, and excretions in a manner that prevents skin and mucous membrane exposures and contamination of clothing, and that avoids transfer of microorganisms to other patients and environments.

Occupational Health and Bloodborne Pathogens

Take care to prevent injuries when using, cleaning, and disposing of sharp instruments.

Never recap used needles, manipulate them using both hands, or use any other technique that involves directing the point of a needle toward any part of the body; rather, use either a one-handed "scoop" technique or a mechanical device designed for holding the needle sheath.

Do not remove used needles from disposable syringes by hand, and do not bend, break, or otherwise manipulate used needles by hand. Place used sharp items in appropriate puncture-resistant containers.

Use mouthpieces, resuscitation bags, or other ventilation devices as an alternative to mouth-to-mouth resuscitation methods in areas where the need for resuscitation is predictable.

Patient Placement

Place a patient who contaminates the environment or who does not (or cannot be expected to) assist in maintaining appropriate hygiene or environmental control in a private room.

DROPLET PRECAUTIONS

Droplet transmission involves contact of the conjunctivae or the mucous membranes of the nose or mouth of a susceptible person with large-particle droplets (larger than 5 µm in size) containing microorganisms generated from the respiratory tract of a person who has a clinical disease or who is a carrier of the microorganism. Droplets are generated from the source person primarily during coughing, sneezing, or talking and during the performance of certain procedures such as suctioning and bronchoscopy.

Transmission via large-particle droplets requires close contact between source and recipient persons, because droplets do not generally travel long distances through the air, thus special air handling and ventilation are not required to prevent droplet transmission.

Mask

In addition to wearing a mask as outlined under Standard Precautions, wear a mask when working within 6-10 ft of the patient. (Logistically, some hospitals may want to implement the wearing of a mask to enter the room.)

Patient Placement

Place the patient in a private room. If a private room is not available, place the patient in a room with a patient(s) who has active infection with the same microorganism but with no other infection (cohorting). When a private room is not available and cohorting is not achievable, maintain spatial separation of at least 3 ft between the infected patient and other patients and visitors and draw the curtain between patient beds. Special air handling and ventilation are not necessary, and the door may remain open.

Patient Transport

Limit the movement and transport of the patient from the room to essential purposes only. If transport or movement is necessary, minimize patient dispersal of droplets by masking the patient.

CONTACT PRECAUTIONS

Direct-contact transmission involves skin-to-skin contact and physical transfer of microorganisms to a susceptible host from an infected or colonized person, such as occurs during patient-care activities that require physical contact. Direct-contact transmission also can occur between two patients (e.g., skin-to-skin contact), with one serving as the source of infectious microorganisms and the other as a susceptible host. Indirect-contact transmission involves contact of a susceptible host with a contaminated intermediate object, an inanimate object or a person, in the patient's environment.

Patient Placement

Place the patient in a private room. If a private room is not available, place the patient in a room with a patient(s) who has active infection with the same microorganism but with no other infection (cohorting).

Gloves and Handwashing

In addition to wearing gloves as outlined under Standard Precautions, wear gloves (clean, nonsterile gloves are adequate) when entering the room.

Change gloves between tasks and procedures on the same patient after contact with material that may contain a high concentration of microorganisms. Remove gloves promptly after use, before touching noncontaminated items and surfaces, and before going to another patient or leaving the room, and wash hands immediately.

After glove removal and handwashing, ensure that hands do not touch potentially contaminated environmental surfaces or items in the patient's room to avoid transfer of microorganisms to other patients or environments.

Gown

In addition to wearing a gown as outlined under Standard Precautions, wear a gown (a clean, nonsterile gown is adequate) when entering the room if you anticipate that your clothing will have substantial contact with the patient, environmental surfaces, or items in the patient's room. Remove the gown before leaving the patient's environment. After gown removal, ensure that clothing does not contact potentially contaminated environmental surfaces to avoid transfer of microorganisms to other patients or environments.

Patient Transport

Limit the movement and transport of the patient from the room to essential purposes only. If the patient is transported out of the room, ensure that precautions are maintained to minimize the risk of transmission of microorganisms to other patients and contamination of environmental surfaces or equipment.

Patient-Care Equipment

When possible, dedicate the use of noncritical patient-care equipment to a single patient (or cohort of patients infected or colonized with the pathogen requiring precautions) to avoid sharing between patients. If use of common equipment or items is unavoidable, then adequately clean and disinfect them before use for another patient.

AIRBORNE PRECAUTIONS

Airborne transmission occurs by dissemination of either airborne droplet nuclei (small-particle residue [5 µm or smaller in size] of evaporated droplets that may remain suspended in the air for long periods of time) or dust particles [5 µm or smaller in size] containing the infectious agent. Microorganisms carried in this manner can be dispersed widely by air currents and may become inhaled by or deposited on a susceptible host within the same room or over a longer distance from the source patient, depending on environmental factors; therefore, special air handling and ventilation are required to prevent airborne transmission.

Patient Placement

Place the patient in a private room that has: 1) monitored negative air pressure in relation to the surrounding areas; 2) 6 to 12 air changes per hour; and 3) appropriate discharge of air outdoors or monitored high-efficiency filtration of room air before the air is circulated to other areas in the hospital. Keep the room door closed and the patient in the room. If a private room is not available, place the patient in a room with a patient who has active infection with the same microorganism but with no other infection (unless otherwise recommended).

Respiratory Protection

Wear respiratory protection (N95 respirator) when entering the room of a patient with known or suspected infection.

Patient Transport

Limit the movement and transport of the patient from the room to essential purposes only. If transport or movement is necessary, minimize patient dispersal of droplet nuclei by placing a surgical mask on the patient, if possible.

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DISCLOSURES TO PUBLIC HEALTH AGENCIES UNDER THE HIPAA PRIVACY POLICY

Covered entities may disclose protected health information (PHI), without individual authorization, to a public health authority legally authorized to collect or receive the information for the purpose of preventing or controlling disease, injury or disability 45 CFR 164.512(b). Further, the Privacy Rule permits covered entities to make disclosures for public health purposes.

Without individual authorization, a covered entity may disclose PHI to a public health authority (or an entity working under a grant of authority) that is legally authorized to collect or receive the information for the purposes of preventing or controlling disease, injury, or disability including, but not limited to:

- Reporting of disease, injury, and vital events (e.g., birth or death)
- Conducting public health surveillance, investigations, and interventions

PHI may also be disclosed without individual authority to:

- Report child abuse or neglect to a public health or other government authority legally authorized to receive such reports
- A person subject to jurisdiction of the Food and Drug Administration (FDA) concerning the quality, safety, or effectiveness of an FDA-related product or activity for which that person has responsibility
- A person who may have been exposed to a communicable disease or may be at risk for contracting or spreading a disease or condition, when legally authorized to notify the person as necessary to conduct a public health intervention or investigation
- An individual's employer, under certain circumstances and conditions, as needed for the employer to meet the requirements of the Occupational Safety and Health Administration, Mine Safety, and Health Administration or similar state law.

TITLE 17. CALIFORNIA CODE OF REGULATIONS, §2500
REPORTABLE DISEASE & CONDITIONS

§2500 REPORTING TO THE LOCAL HEALTH AUTHORITY

§2500 (b)

It shall be the duty of every health care provider, knowing of or in attendance on a case or suspected case of any of the diseases or conditions listed, to report to the local health officer for the jurisdiction where the patient resides. Where no health care provider is in attendance, any individual having knowledge of a person who is suspected to be suffering from one of the diseases or conditions listed may make such a report to the local health officer for the jurisdiction where the patient resides.

§2500 (c)

The administrator of each health facility, clinic or other setting where more than one health care provider may know of a case, a suspected case or an outbreak of disease within the facility shall establish and be responsible for administrative procedures to assure that reports are made to the local health officer.

§2500 (a)(14)

'Health care provider' means a physician and surgeon, a veterinarian, a podiatrist, a nurse practitioner, a physician assistant, a registered nurse, a nurse midwife, a school nurse, an infection control practitioner, a medical examiner, a coroner, or a dentist.

Excerpted from the California Code of Regulations
Available at: ccr.oal.ca.gov

San Francisco Department of Public Health
Health Alert Notification Database

The San Francisco Department of Public Health (SFDPH) periodically sends Health Alerts, Advisories, and Updates to San Francisco clinicians. Health Alerts provide important, timely information on the recognition, diagnosis, management, and reporting of communicable disease threats. Recent Health Alert topics have included measles, botulism, MRSA and influenza.

SIGN UP TO RECEIVE HEALTH ALERTS
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- Fax contact information to: (415) 554-2848

  OR
- Mail contact information to: Health Alert Notification Database Coordinator
  San Francisco Department of Public Health
  101 Grove Street, Room 408
  San Francisco, CA 94102

  OR
- Complete our online form at: www.sfcdcp.org/registerforalert

Name: _____ Degree: _____

Title: _____ Specialty:_____

Company/Organization: _____

Department: _____

Address: _____

City: _____ Zip: _____

Business Fax: _____ Business Phone: _____

Pager: _____ Mobile: _____

Email: _____

Note: All contact information provided to SFDPH is kept confidential.

Communicable Disease Control & Prevention
101 Grove Street, Room 408 • San Francisco, CA 94102
Phone: (415) 554-2830 • Fax: (415) 554-2848 • http://www.sfcdcp.org

CITY AND COUNTY OF SAN FRANCISCO
PUBLIC HEALTH LABORATORY
101 Grove Street, Room 419
San Francisco, CA 94102
Sally Liska, Dr. P.H., Lab Director
Tel: (415) 554-2800 Fax: (415) 431-0651
CLIA ID # 05D0643643

For Laboratory Use Only

_____ Laboratory Number

_____ Date/Time Received

PLEASE ATTACH PRE-PRINTED LABEL or PRINT CLEARLY

Patient's Name: _____ (Last, First) Gender: ____ DOB: _____ Race/Ethnicity: _____

Address: _____ Phone: _____

City / State: _____ Zip Code: _____

Submitted By: _____ (Clinic) Requesting Clinician: _____

Medical Record #: _____ **Medi-Cal/HAP #:** _____ S-Code #: _____

Bill To: ☐ Submitter ☐ Medi-Cal ☐ Family Planning ☐ Private Pay

CHECK BOTH SOURCE AND TEST REQUESTED; INDICATE DATE COLLECTED

SPECIMEN SOURCE: **DATE SPECIMEN TAKEN:** _____

☐ Blood	☐ Urine	☐ Rectal	☐ Throat	☐ Rash/Lesion	☐ Culture
☐ Serum	☐ Cervix	☐ Feces	☐ Sputum	☐ CSF	☐ Slide
☐ Plasma	☐ Urethral	☐ Genital	☐ Nasopharyngeal	☐ Oral Fluid	☐ Other: _____

BACTERIOLOGY

☐ Gonorrhea Screen

☐ Enteric Screen

☐ Special Bacteriology Culture

☐ Clearance for: _____

☐ Other: _____

PARASITOLOGY

☐ Ova and Parasites

☐ Clearance for: _____

☐ Blood Smear (e.g. Malaria)**

☐ Cryptosporidia

☐ Cyclospora

☐ Other: _____

MYCOBACTERIA

☐ Quantiferon (TB infection blood test)*

A reason for Quantiferon testing MUST be checked:

☐ Immunocompromised
☐ TB suspect ☐ Foreign-born
☐ Contact to TB ☐ Homeless
☐ Diabetes ☐ IVDU
☐ Renal failure ☐ Program clearance
☐ School clearance (US born)
☐ Other _____

☐ Acid Fast Smear

☐ Specimen for Isolation

☐ Culture for Identification

☐ TB Susceptibility

☐ Direct Amplification Test

HIV VIRAL LOAD (bDNA)*

☐ Time Collected: _____

CHLAMYDIA AND GONORRHEA

☐ Chlamydia

☐ Gonorrhea

A reason for CT/GC testing MUST be checked:

☐ Age ≤25 ☐ MSM screen
☐ Prior CT/GC Infection ☐ Pregnant
☐ Cervicitis/Urethritis ☐ IUD
☐ Contact to STD
☐ Other_____

SEROLOGY

☐ Syphilis - VDRL ☐ Syphilis - TP-PA

☐ Rubella IgG ☐ Hepatitis C Antibody

☐ Herpes Simplex-2 ☐ Other: _____

VIROLOGY

☐ Herpes Culture

☐ Other: _____

Comment: _____

_____

*** Specimens have time limitations for submission. Contact laboratory for details.**
****Travel History Required**

CONFIDENTIAL MORBIDITY REPORT

NOTE: For STD, Hepatitis, or TB, complete appropriate section below. Special reporting requirements and reportable diseases on back.

DISEASE BEING REPORTED: _____

Patient's Last Name

Social Security Number ___ — ___ — ___

First Name/Middle Name (or initial)

Birth Date Month Day Year

Age

Address: Number, Street **Apt./Unit Number**

City/Town **State** **ZIP Code** **Country of Birth**

Area Code **Home Telephone** **Gender** M F **Pregnant?** Y N Unk **Estimated Delivery Date** Month Day Year

Area Code **Work Telephone**

Patient's Occupation/Setting

❒ Food service ❒ Day care ❒ Correctional facility
❒ Health care ❒ School ❒ Other _____

Ethnicity (✓ one)

❒ Hispanic/Latino
❒ Non-Hispanic/Non-Latino

Race (✓ one)

❒ African-American/Black
❒ Asian/Pacific Islander **(✓ one)**
- ❒ Asian-Indian ❒ Japanese
- ❒ Cambodian ❒ Korean
- ❒ Chinese ❒ Laotian
- ❒ Filipino ❒ Samoan
- ❒ Guamanian ❒ Vietnamese
- ❒ Hawaiian ❒ Other_____

❒ Native American/Alaskan Native
❒ White: _____
❒ Other: _____

DATE OF ONSET Month Day Year

DATE DIAGNOSED Month Day Year

DATE OF DEATH Month Day Year

Reporting Health Care Provider

Reporting Health Care Facility

Address

City **State** **ZIP Code**

Telephone Number ( )

Fax ( )

Submitted by

Date Submitted (Month/Day/Year)

REPORT TO

Communicable Disease Control Unit
San Francisco Dept of Public Health
101 Grove Street, Room 408
San Francisco, CA 94102

PHONE: (415) 554-2830

FAX: (415) 554-2848

STD (Fax): (415) 431-4628
TB (Fax): (415) 648-8369
AIDS/HIV (PH): (415) 554-9050

(Obtain additional forms from your local health department.)

SEXUALLY TRANSMITTED DISEASES (STD)

Syphilis

❒ Primary (lesion present)
❒ Secondary
❒ Early latent < 1 year
❒ Latent (unknown duration)
❒ Late latent > 1 year
❒ Late (tertiary)
❒ Congenital
❒ **Neurosyphilis**

Syphilis Test Results

❒ RPR Titer:_____
❒ VDRL Titer:_____
❒ FTA/MHA: ❒ Pos ❒ Neg
❒ CSF-VDRL: ❒ Pos ❒ Neg
❒ Other:_____

❒ **Chlamydia**
❒ **Gonorrhea**
❒ **Chancroid**

Site:
❒ Pharyngeal ❒ Urethral/Cervical
❒ PID ❒ Urine
❒ Rectal ❒ Other: _____

Gender of Sex Partners last 12 months:
❒ Male ❒ Transgender (M to F)
❒ Female ❒ Transgender (F to M)
❒ Unknown ❒ Refused

STD TREATMENT INFORMATION

❒ **Treated (**Drugs, Dosage, Route **):**

_____
_____

Date Treatment Initiated Month Day Year

❒ **Untreated**
❒ Will treat
❒ Unable to contact patient
❒ Refused treatment
❒ Referred to: _____

VIRAL HEPATITIS

		Pos	Neg	Pend	Not Done
❒ **Hep A**	anti-HAV IgM	❒	❒	❒	❒
❒ **Hep B**	HBsAg	❒	❒	❒	❒
❒ **Acute**	anti-HBc	❒	❒	❒	❒
❒ **Chronic**	anti-HBc IgM	❒	❒	❒	❒
	anti-HBs	❒	❒	❒	❒
❒ **Hep C**	anti-HCV	❒	❒	❒	❒
❒ **Acute** ❒ **Chronic**	PCR-HCV	❒	❒	❒	❒
❒ **Hep D (Delta)**	anti-Delta	❒	❒	❒	❒
❒ **Other:** _____		❒	❒	❒	❒

Suspected Exposure Type

❒ Blood transfusion ❒ Other needle exposure ❒ Sexual contact ❒ Household contact
❒ Child care ❒ Other: _____

TUBERCULOSIS (TB)

Status

❒ **Active Disease**
- ❒ Confirmed
- ❒ Suspected

❒ **Infected, No Disease**
- ❒ Convertor
- ❒ Reactor

Site(s)

❒ Pulmonary
❒ Extra-Pulmonary
❒ Both

Mantoux TB Skin Test

Date Performed Month Day Year

Results:_____ mm ❒ Pending ❒ Not Done

Chest X-Ray

Date Performed Month Day Year

❒ Normal ❒ Pending ❒ Not done
❒ Cavitary ❒ Abnormal/Noncavitary

Bacteriology

Date Specimen Collected Month Day Year

Source _____

Smear: ❒ Pos ❒ Neg ❒ Pending ❒ Not done
Culture: ❒ Pos ❒ Neg ❒ Pending ❒ Not done

Other test(s) _____

TB TREATMENT INFORMATION

❒ **Current Treatment**
❒ INH ❒ RIF ❒ PZA
❒ EMB ❒ Other: _____

Date Treatment Initiated Month Day Year

❒ **Untreated**
❒ Will treat
❒ Unable to contact patient
❒ Refused treatment
❒ Referred to: _____

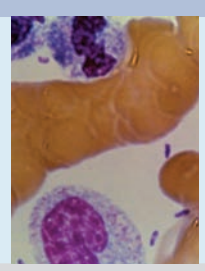
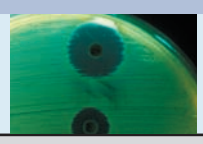
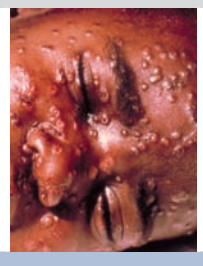
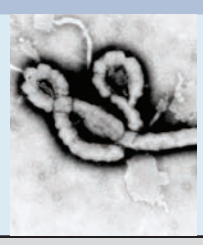
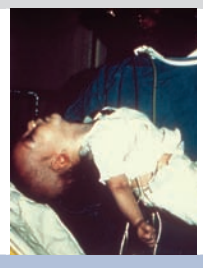
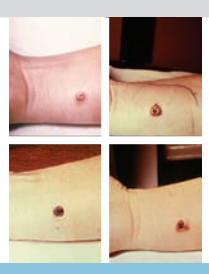
REMARKS

Bioterrorism Syndromes

If you suspect disease that may be bioterrorism related, IMMEDIATELY call SFDPH Communicable Disease Control Unit.

24/7 TELEPHONE: (415) 554-2830 (After-hours: follow prompts to page on-call MD)

For SF patients and clinical institutions San Francisco Department of Public Health (SFDPH) can facilitate reference lab testing and prophylaxis; can provide treatment and infection control guidelines; and can activate emergency responses.

Syndrome	Bioterrorism Threat Disease Description	Differential Diagnosis	Picture	Initial Lab & Other Diagnostic Test Results	Immediate Public Health & Infection Control Actions
ACUTE RESPIRATORY DISTRESS WITH FEVER	**Inhalational Anthrax**				
	Abrupt onset of fever, chest pain, respiratory distress, no history of trauma or chronic disease, progression to shock and death within 24-36 hours.	Dissecting aortic aneurysm, pulmonary embolism, influenza.		Chest x-ray with widened mediastinum; gram-positive bacilli in sputum or blood. Reference testing available through SFDPH. Call SFDPH immediately.	Call SFDPH immediately. Alert your laboratory to possibility of anthrax. No person-to-person transmission. Infection control: standard precautions.
	Pneumonic Plague				
	Apparent severe community-acquired pneumonia but with hemoptysis, cyanosis, gastrointestinal symptoms, shock.	Community-acquired pneumonia, Hantavirus pulmonary syndrome, meningococcemia, rickettsiosis, influenza.		Gram-negative bacilli or coccobacilli in sputum, blood or lymph node; safety pin appearance with Wright or Giemsa stain. Reference testing through SFDPH. Call SFDPH immediately.	Call hospital infection control and SFDPH immediately. Ask family members/close contacts of patient to stay at hospital for public health interview/ prophylaxis; get detailed address and phone info. Alert laboratory of possibility of plague. Infection control: **droplet** precautions in addition to standard precautions.
	Ricin (aerosolized)				
	Acute onset of fever, chest pain and cough, progressing to respiratory distress and hypoxemia; not improved with antibiotics, death in 36-72 hours.	Plague, Q fever, Staphylococcal enterotoxin B, phosgene poisoning, tularemia, influenza.		Chest x-ray with pulmonary edema. Reference testing through SFDPH. Call SFDPH immediately.	Call SFDPH immediately. Infection control: standard precautions.
	Staphylococcal enterotoxin B				
	Acute onset of fever, chills, headache, nonproductive cough and myalgia (influenza-like illness) with a NORMAL chest x-ray.	Influenza, adenovirus, mycoplasma, ricin.		Primarily clinical diagnosis. Reference testing through SFDPH. Call SFDPH immediately.	Call SFDPH immediately. Infection control: standard precautions.
ACUTE RASH WITH FEVER	**Smallpox**				
	Papular rash with fever that begins on the face and extremities and uniformly progresses to vesicles and pustules; headache, vomiting, back pain, and delirium common.	Varicella, disseminated herpes zoster, vaccinia, monkeypox, cowpox.		Clinical diagnosis with laboratory confirmation. Call SFDPH immediately. After calling SFDPH, vaccinated, gowned and gloved person obtains specimens (scabs or swabs of vesicular or pustular fluid). Reference testing available through SFDPH.	Call hospital infection control and SFDPH immediately. Ask family members/close contacts of patient to stay at hospital for public health interview and vaccination; get detailed address and phone info. Infection control: **airborne** and **contact** precautions in addition to standard precautions.
	Viral Hemorrhagic Fever (e.g., Ebola, Marburg)				
	Fever with mucous membrane bleeding, petechiae, thrombocytopenia and hypotension in a patient without underlying malignancy.	Meningococcemia, malaria, typhus, leptospirosis, borreliosis, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS).		Reference testing available through SFDPH. Call SFDPH immediately.	Call hospital infection control and SFDPH immediately. Ask family members/close contacts of patient to stay at hospital for public health interview and follow-up; get detailed address and phone info. Infection control: **contact** precautions in addition to standard precautions.
NEUROLOGIC SYNDROMES	**Botulism**				
	Acute bilateral descending flaccid paralysis beginning with cranial nerve palsies.	Guillain-Barré syndrome, myasthenia gravis, Eaton-Lambert myasthenic syndrome, midbrain stroke, tick paralysis, Mg++ intoxication, organophosphate, carbon monoxide, paralytic shellfish, or belladonna-like alkaloid poisoning, polio.		CSF protein normal; EMG with repetitive nerve stimulation shows augmentation of muscle action potential. Toxin assays available through SFDPH. Call SFDPH immediately.	Request botulinum antitoxin from SFDPH immediately. Infection control: standard precautions.
	Encephalitis (Venezuelan, Eastern, Western)				
	Encephalopathy with fever and seizures and/or focal neurologic deficits.	Herpes simplex, post-infectious, other viral encephalitides.		Reference testing available through SFDPH. Call SFDPH immediately.	Call SFDPH immediately. Infection control: standard precautions.
INFLUENZA-LIKE ILLNESS	**Brucellosis**				
	Irregular fever, chills, malaise, headache, weight loss, profound weakness and fatigue, anorexia, nausea, vomiting, diarrhea, lymphadenopathy, hepatosplenomegaly, arthralgias and arthritis especially in large joints: sacroiliitis, paravertebral abscesses. May have cough and pleuritic chest pain.	Numerous diseases, including Q Fever, tularemia.		Tiny, slow-growing, faintly-staining, gram-negative coccobacilli in blood or bone marrow culture. Leukocyte count normal or low. Anemia, thrombocytopenia possible. CXR nonspecific: normal, bronchopneumonia, abscesses, single or miliary nodules, enlarged hilar nodes, effusions. Reference testing available through SFDPH. Call SFDPH immediately.	Notify your laboratory if brucellosis suspected--microbiological testing should be done in a biological safety cabinet to prevent lab-acquired infection. Call SFDPH immediately. Infection control: standard precautions.
	Tularemia				
	Fever, chills, rigors, headache, myalgias, coryza, sore throat initially; followed by weakness, anorexia, weight loss, lymphadenopathy. Substernal discomfort, dry cough if pneumonic disease.	Numerous diseases, including Q Fever, brucellosis.		Small, faintly-staining, slow-growing, gram-negative coccobacilli in smears or cultures of sputum, blood. CXR may show infiltrate, hilar adenopathy, effusion. Reference testing available through SFDPH. Call SFDPH immediately.	Notify your laboratory if tularemia suspected-- microbiological testing should be done in a biological safety cabinet to prevent lab-acquired infection. Call SFDPH immediately. Infection control: standard precautions.
CUTANEOUS ULCER	**Cutaneous Anthrax**				
	Papule that progresses to vesicle or bulla in 1-2 days, sometimes hemorrhagic or with satellite lesions; vesicle ulcerates and central black eschar forms in 3-7 days; painless; surrounding erythema; edema; may have regional lymphadenopathy, fever, headache or malaise.	Spider bite, furunculosis, ecthyma, ecthyma gangrenosum, orf.		Gram stain and culture of skin lesion (unroofed vesicle fluid, base of ulcer, edges of/ underneath eschar); blood cultures; punch biopsy if patient on antimicrobials or if gram stain and culture are negative and clinical suspicion is high.	Call SFDPH immediately. Alert your laboratory to possibility of anthax. Infection control: standard precautions.

Adapted from California State and Local Health Department Bioterrorism Surveillance and Epidemiology Working Group, 2001

Rev. 7/05

Also call SFDPH for routine disease reporting

Phone: (415) 554-2830 Fax line: (415) 554-2848 E-mail: cdcontrol@sfdph.org

www.sfdph.org/cdcp