

The coming Germ Warfare

Horrible new viruses are emerging from the rain forests

More disturbing: Old killers like TB and malaria are back, and TB is out of control.

CHICAGO TRIBUNE

MANAUS, Brazil — It starts with a fever, like a hundred less deadly plagues.

Then comes a growing weakness. The skin turns yellow. In the abdomen, internal bleeding begins. Soon, blood pours from the body, through the eyes and in the endless black vomit. In nine of 10 cases, the liver dissolves. The victim dies.

It's not Ebola. It's Labrea black fever, just one of a half-dozen deadly and little-understood viral diseases emerging from the rain forests of Latin America.

"People all the time are going to the jungle and coming back with strange fevers no one knows about," said Betsy Dutary Thatcher, a malaria specialist at Brazil's National Institute for Amazon Research in Manaus. "If we started looking for them, we could isolate a new variety every week."

"Viruses are the unknown frontier. Adib Jatene said we could have things here worse than Ebola, and he's absolutely right."

The reasons aren't clear, but poverty is a huge problem in Latin America, as is the slow failure of health-care and disease prevention programs. Human migration and that of rodents, pushed out by humans, also have contributed to the spread of disease.

Perhaps never has the battle against disease looked so bleak as it does right now in Latin America and in much of the Third World. Across the planet, new diseases are appearing at a frightening pace, researchers say. Even more disturbing, scourges once thought relegated to history are making a

comeback, particularly in Latin America.

Tuberculosis, thought conquered after the introduction of new drugs in the 1940s, has roared back and is spreading out of control. A third of the world's population is now infected with the bacteria, according to the World Health Organization.

Most carriers never develop TB; but just this year 8.8 million people have gotten tuberculosis, and 3 million will die from it.

Malaria, one of the world's oldest plagues, also is making a comeback. Latin America reported more than a million new cases last year, half of them in Brazil. Mefloquine, the drug most effective in preventing the deadliest form of malaria — that caused by the *Plasmodium falciparum* parasite — is beginning to fail as the mosquito-borne parasites develop resistance, Thatcher said.

"I work with mosquitoes, and I'm terribly afraid," she said.

But it is the lesser-known diseases and new plagues that have grabbed the headlines regularly in Latin America this year.

In Nicaragua and Honduras, a mystery illness characterized by chills, fever and severe bleeding in the lungs has been tentatively identified as leptospirosis, an animal disease contracted through contact with animal waste. The outbreak

has killed 16 people and sickened more than 2,000 in the two countries over the past two months. A similar outbreak in Brazil killed more than 40 people in February.

In Colombia, an apparent outbreak of mosquito-borne equine encephalitis killed at least 26 people and forced 13,000 others to seek treatment in September.

In Mexico and across much of Latin America, dengue fever, characterized by high fever and intense body pain, has struck nearly 200,000 people this year and is threatening to move into the United States. A deadly variant of the disease, dengue hemorrhagic fever, has stricken another 3,500 people.

Scientists stumped by new, deadly virus that has hit Malaysia

Health officials believe disease that killed at least 111 is spread from pigs to humans

ASSOCIATED PRESS

KUALA LUMPUR, Malaysia — A tropical virus that has killed dozens of people in Malaysia is the first of its kind, and virologists are stumped as to how it spreads, an American health official said Thursday.

Nine scientists from the United States and other experts from Australia, Taiwan and Japan arrived in Malaysia several weeks ago to help the Southeast Asian country determine the nature of the virus believed to be spreading from pigs to humans.

The CDC said Thursday that 229 people are believed to have been sickened in the past six months in Malaysia. At least 111 have died.

"This is a new, previously unrecognized virus found in humans," said Tom Skinner, a spokesman for the U.S. Centers of Disease Control and Prevention in Atlanta. "This virus has never been seen before."

The scientists have been tramping through pig pens and farming communities where the deadly virus first appeared, wearing gloves, gowns and battery-operated respirators while visiting the worst-hit areas.

"We don't know if it's highly infectious. We don't know how people are being infected," Skinner said. "It doesn't appear, right now, that this is being transmitted from person to person, but we're still not going to rule that out."

Government health experts initially said the outbreak began with the deaths of 15 people in October who succumbed to the Japanese encephalitis virus, which is transmitted by the Culex mosquito. These findings were confirmed by World Health Organization officials from Japan, who came to

help investigate.

But in late February, the number of deaths among villagers and farmers in the hog-rearing district of Bukit Pelandok in central Negeri Sembilan jumped dramatically, prompting health officials to seek further help.

Malaysian virologists flew to the United States on March 17 with samples. Lab analyses quickly proved that the virus wasn't Japanese encephalitis. Instead, it resembled a very rare Hendra virus, first detected in Australia in 1994.

Symptoms are the same for both viruses — high fever, aches,

Soldiers swept through pig-farming districts in an attempt to slaughter 1 million pigs.

eventual coma and death.

It's not clear what proportion of the illnesses were caused by infections with the new Hendra-like virus or how many were due to Japanese encephalitis, the CDC said.

The CDC finding plunged Malaysia into further confusion. Pig farmers deserted their homes after police cordoned off their villages. To curb the outbreak, soldiers dressed like astronauts swept through a half-dozen pig-farming districts in an attempt to slaughter 1 million pigs.

A 24-hour government hot line set up Wednesday provides detailed information on the Hendra virus. It encourages all workers on pig farms to wash their hands after handling pigs.

At conference, scientists report spread of resistant AIDS strain

Protease inhibitors used in cocktail treatments don't affect it.

ASSOCIATED PRESS

GENEVA — For the first time, doctors are reporting the spread of a strain of the AIDS virus that is resistant to the key medicines that have revolutionized care of the disease over the past two years.

AIDS viruses have long circulated that are impervious to AZT and other older AIDS medicines. But now people are beginning to catch viruses that are also resistant to protease inhibitors, the pivotal ingredients of the drug cocktails that have made AIDS a survivable disease.

These infections will almost certainly be difficult and perhaps impossible to treat — at least with the medicines now on the market, doctors say in a report to be released Wednesday at the 12th International AIDS Conference.

Some believe that the availability of AIDS treatment with protease inhibitors has made some people less diligent about safe-sex practices to prevent infection.

"This is a wakeup call to people who assume that since we have adequate therapy, if they get infected they will be easily treated," said Dr. Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases.

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At the conference, San Francisco doctors reported one new infection with a highly resistant virus, while a Swiss team said they had seen several more. No one knows yet how common these untreatable strains are.

The San Francisco case was described by Dr. Frederick Hecht of the University of California, San Francisco.

The patient, a middle-aged San Francisco man, caught the virus last fall. He was infected by a man whose own infection was diagnosed in 1990 and had taken many different AIDS drugs off and on, including protease inhibitors.

The man's virus is resistant to four different protease inhibitors, plus the drugs AZT and 3TC.

"We are seeing the emerging edge of a new aspect of the epidemic," Hecht said. "These people are at high risk of failing treatment right from the outset."

From the start of treatment with the three-drug cocktails, doctors have worried about the spread of resistant strains. Following the regimens means taking 15 or 20 pills a day on a precise schedule. Missing even a few doses allows mutant viruses to emerge that are resistant to protease inhibitors.

Until now, some experts wondered if these protease-resistant viruses might spread poorly because their mutations inhibited their ability to reproduce.

Hecht said doctors first became concerned about the San Francisco patient after he responded much more slowly than usual to drug treatment. After learning his virus was resistant to the drugs, he stopped therapy entirely but is still healthy.

A report on the case will be published later this month in the New England Journal of Medicine.

The Swiss cases were reported at the conference by Dr. Sabine Yerly and others from University Hospital in Geneva.

Three countries have stocks of smallpox, U.S. intelligence says

THE NEW YORK TIMES

A secret federal intelligence assessment completed earlier this year concludes that Iraq, North Korea and Russia are probably concealing the deadly smallpox virus for military use, government officials say.

The assessment, the officials say, is based on evidence that includes disclosures by a senior Soviet defector, blood samples from North Korean soldiers that show recent smallpox vaccinations, and the fairly recent manufacture of smallpox vaccine by Iraq.

The officials say the warning was a deciding factor in President Clinton's recent decision to reverse course and forgo destruction of U.S. stocks of the virus.

Besides the United States, only Russia retains openly declared stocks of the virus now, nearly 20 years after the disease was declared to be eradicated. The intelligence assessment concludes that Russia is most likely hiding additional stocks of the virus at military sites.

Although the United States has about 56,000 troops stationed near Iraq and North Korea and is periodically bombing Iraq, the officials say there appears to be no imminent military threat involving the virus.

The virus that causes smallpox is known as variola. For ages, it ravaged the globe, killing millions and crippling many survivors. Victims had high fever, nausea and a pronounced rash that left survivors with permanently pocked skin. The disease was highly contagious and quick to attack anyone without immunity, making it one of history's great killers.

The United States unilaterally renounced germ warfare in 1969 and lobbied for a 1972 international treaty banning such arms that more than 100 nations signed.

Iraq and North Korea have repeatedly denied that they have programs to develop germ weapons and both are signatories of the 1972 treaty. And Mikhail A. Shurgalin, a spokesman at the Russian Embassy in Washington, denied that Russia maintains secret military stocks of smallpox. "We always observe our international commitments," he said, "including those relating to bacteriological weapons."

The warning was based on an analysis of years of accumulated data, say the officials, and was prompted by a White House review of whether U.S. stocks of the smallpox virus should be destroyed by the end of this month, as a panel of the World Health Organization recommended in 1996. The United States had previously sided with many other nations in urging that destruction.

The new intelligence assessment, officials said, helped persuade a team of presidential advisers to unanimously urge Clinton to delay the virus' destruction, a reversal the White House announced on April 22.

A senior Defense Department official familiar with the assessment said that destroying the virus at the two official repositories, in Russia and the United States, and declaring it abolished globally would be "perpetrating a fraud."

Another key factor in Clinton's decision, officials said, was a report by the National Academy of Sciences concluding that keeping the virus would speed the development of new anti-viral drugs and treatments.

In recent years, U.S. experts have clashed bitterly over whether the virus exists outside the two official repositories, with intelligence experts tending to argue that it does. Covert stocks would undermine the global plan to exterminate the microbe, and the very existence of hidden stockpiles would be a signal that the countries holding them are interested in the development of germ weapons for war or terrorism.

Outside of the lab, variola survives only within the human body. After world health authorities declared humans free of smallpox in 1980, plans were made to destroy laboratory stocks. The cause of the ancient pestilence was to be the world's first species made extinct by design rather than accident.

Today, declared stocks exist only in guarded freezers at the Centers for Disease Control and Prevention in Atlanta and the Russian State Research Center of Virology and Biotechnology (known as Vector) near Novosibirsk, in Siberia.

The officials who discussed the new intelligence warning refused to divulge it in its entirety. But in a series of interviews, they disclosed some details and pointed out supporting evidence scattered among declassified intelligence reports.

Considerable weight, they said, was given to the disclosures of a Soviet defector, Ken Alibek. Alibek came to the United States in 1992, after serving as a top official in the Soviet Union's illicit germ warfare program, now known to have been the world's largest and most advanced. Russian President Boris Yeltsin ordered it to end in 1992.

In secret debriefings, Alibek said that Russia had grown vast

WHAT IT MEANS TO YOU

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quantities of the smallpox virus for war and that, as Russian scientists sought new ways to support themselves when the Soviet system collapsed, samples of the virus might have been sold or hidden.

Iraq is well known to have worked hard at using germs in unconventional arms — the vi-

rus could most easily be spread by some form of spraying. But the United Nations, which probed Iraq after the 1991 Persian Gulf War, never listed smallpox as a focus of Iraq's biological weapons programs.

Infectious diseases are on the rise, doctors say

WASHINGTON — Infectious diseases are on a global rebound, killing thousands more Americans, surviving potent antibiotics and possibly evolving into stronger bugs as the climate changes, a coalition of doctors warned Tuesday.

The world is "more vulnerable than ever before," said Nobel laureate Joshua Lederberg, who led a call by the Journal of the American Medical Association and 35 other international medical journals for a global battle against infections.

Tuesday, doctors in 21 countries published 242 studies to illustrate the scope of the threat. Among the most alarming: The U.S. death rate from infectious diseases rose 58 percent between 1980 and 1992, and a snapshot of middle America found antibiotic resistance growing fast. That doesn't mean people should panic, Lederberg emphasized. Instead, the findings should persuade world governments and drug makers to fund research to fight back — and doctors to stop overprescribing antibiotics.

SMALLPOX

Panel: Virus stocks would help counter possible terrorism

WASHINGTON — Smallpox has been eradicated worldwide, but U.S. experts say laboratory specimens of the virus should be preserved to make vaccines in case the deadly disease is ever used as a bioterrorist weapon.

Smallpox cursed humanity with disease, death and disfigurement for more than 1,000 years but was wiped out as a naturally occurring disease in 1980 after a worldwide inoculation effort.

The World Health Organization has recommended destroying, by this June, two caches of specimens that were believed to remain, one in Russia, the other in the United States.

But bioterrorism experts have said in recent months they believe the virus has been distributed to other spots in Russia, perhaps in places with less effective security controls.

GEORGIA

9 dead, 3 stillborn from bacteria in hot dogs, cold cuts

ATLANTA — A bacterial outbreak linked to a Michigan meat processing plant has killed nine people and caused three stillbirths, the Centers for Disease Control and Prevention said Friday.

The outbreak has sickened more than 60 people in 12 states since August, the centers said.

Sara Lee, parent company of the Bil Mar Foods plant in Zeeland, Mich., recalled several brands of hot dogs and cold cuts last month after the centers found listeria contamination in packs of hot dogs and deli meat.

1998: A Year of Disasters

The year just past brought approximately 700 catastrophic natural disasters, which killed at least 50,000 people—making 1998 the most calamitous year on record, according to Munich Reinsurance, a German company that monitors natural disasters. Last year's total was *three times* the annual average for natural catastrophes during the 1960s.

Among the worst of this worst year: 240 windstorms, 170 floods and nine hurricanes (Mitch killed an estimated 9200 people, cost \$5 billion in uninsured losses and \$150 million in insured losses). There also was a typhoon in Japan, an earthquake in Afghanistan, a cyclone in India, mudslides in Italy, winter storms and a cold wave in Europe, heat waves and forest fires in the U.S., Greece and Brazil. (And we didn't even mention the mess in Washington, D.C.)

Experts warn deadly germ becoming drug-resistant

FROM WIRE REPORTS

ATLANTA — A staph germ that causes thousands of often deadly infections among hospital patients each year is becoming resistant to medicine's drug of last resort and appears to be on the brink of becoming unstoppable.

The possibility of a widespread, untreatable bacterial infection has not been known since penicillin became widely used in the 1940s.

The new strain of staphylococcus aureus bacteria that was discovered in a four-month-old Japanese infant showed resistance for the first time against vancomycin, an antibiotic that has been around since 1970 and is used when other drugs fail.

The strain has not yet reached U.S. hospitals, but health experts said it is only a matter of time.

A KILLER

■ STAPH BACTERIA ARE THE NO. 1 CAUSE OF HOSPITAL INFECTIONS IN THE U.S. THE INFECTIONS KILL 60,000 TO 80,000 PEOPLE EACH YEAR.

In the meantime, the Centers for Disease Control and Prevention and other experts said, hospitals need to tighten their practices to prevent the spread of germs, and doctors should use antibiotics

more sparingly. Pharmaceutical companies are already working on new antibiotics.

"We have a situation which is very worrisome," said Fred Tenover, a microbiologist who is laboratory chief of the CDC's hospital infections branch. He said that

PARTIAL

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Infectious diseases feed on global complacency

By Steve Sternberg
USA TODAY

WASHINGTON — Mankind has dangerously miscalculated the threat posed by bacteria and viruses to millions of lives, national security and world economic development, says a report out Thursday.

The report, by the World Health Organization (WHO), offers its most scathing portrait ever of global complacency about the potential spread of infectious diseases. And with global travel increasing, the report says, "the prospects for containing future outbreaks are decreasing."

"The minute we let down our guard, infectious diseases come back," says David Heymann, WHO director of infectious disease control.

In the decades since the advent of antibiotics led to premature claims of victory, infectious diseases are still killing 13 million people a year, half in prosperous countries. Last year, 180,000 people died of infections in the USA alone.

Just six ailments — AIDS, tuberculosis, malaria, measles, diarrheal disease and pneumonia — killed 80% of those who died before their 44th birthday in 1988.

"We live in a global village. We can't afford to ignore crises that occur in other parts of the world because they will impact us," says Jim Hughes, director of infectious disease for the federal Centers for Disease Control and Prevention (CDC).

All of these diseases are preventable, most extremely cheaply. Yet governments spend 60 times as much on armaments as on disease prevention.

Six times as many people have died of AIDS, malaria and tuberculosis than in all the military conflicts of the last 50 years, the report says.

The WHO says roughly 150 million people have died of these diseases since 1945, compared with 23 million who have died in combat. In the USA, at least 5 million people have died of infectious diseases during that period.

Resistance to antibiotics is adding to that toll, the report says. TB drugs no longer work effectively in one of five patients in Eastern Europe, anti-malaria drugs have lost much of their punch in Asia and Africa, and most other germs learn to thrive in the presence of mankind's deadliest antibiotics.

That trend will continue until better antibiotics are made and existing antibiotics are used more wisely, experts say.

New diseases, including AIDS, hepatitis C, hantavirus and ebola, continue to emerge. Heymann also says that the spread of drug-resistant bacteria and international travel will make it harder to control diseases. "The window of opportunity is closing," he says.

Supergerm resists drugs, may have killed man

ASSOCIATED PRESS

NEW YORK — A supergerm that has proved resistant to one of the most potent antibiotics available may have claimed its first victim.

A man in his 70s died last month at a hospital after becoming infected with a strain of staphylococcus aureus bacteria, or staph.

"Because his family did not permit an autopsy, it's possible the man died from his kidney ailment. But his body also had been invaded by the resistant germs, and "it's very likely he died from that," said Kristine Smith, a state Health Department spokeswoman.

"The patient was already extremely ill, and that may have contributed to his inability to fight the infection," Smith added.

Many people have the germ, and it's usually harmless. But when it mutates into a strain impervious to some antibiotics, it can be dangerous, especially to patients in hospitals, where staph is the No. 1 cause of infections.

State Health Commissioner Barbara DeBuono said the man's death was an isolated case that posed no danger to the public. The victim's family, hospital workers and other patients were tested and declared safe.

The unidentified man was one of four known cases in the world in which staph proved resistant to

the antibiotic vancomycin.

In the three other known cases, the patients all survived after being treated with a cocktail of other antibiotics. The first case was that of a child in Japan who became ill in 1996. Last year, another case was reported in New Jersey and a third in Michigan.

For several years, doctors have been warning of the emergence of drug-resistant bacteria. The problem is attributed to overuse or misuse of antibiotics.

For the past dozen years or so, with the effectiveness of other antibiotics weakened by frequent use, vancomycin has become the drug of choice for treating staph. But along with increased use comes increased resistance.

The Centers for Disease Control and Prevention warned hospitals around the country last summer that more cases of the resistant strain may be on the way as antibiotics are overused and the bacteria develop immunity.

An experimental French drug called Synercid could prove to be an effective new remedy.

In the meantime, many hospitals have restricted use of their most potent antibiotics, isolated their sickest patients and instructed staff members to wash their hands often.

However, many doctors fear the time is coming when there will

be no alternative antibiotic to turn to — for the first time since antibiotics hit the market in the 1950s.

Staph bacteria are blamed for about 13 percent of the nation's 2 million hospital infections each year, including skin infections and pneumonia, according to the CDC. Overall, infections kill 60,000 to 80,000 people.

Plague as a Weapon of War

Col. Byron Weeks, M.D., Ret.

Wednesday, Oct. 17, 2001

Dr. Weeks has had a distinguished medical and military career with the U.S. Air Force Medical Corps. He began military service as the youngest flight surgeon in the U.S. Air Force during the Korean War. After 15 years of military service, during which he served in senior posts, including Hospital Commander at Bitburg Air Force Base, Germany, Dr. Weeks retired and entered private practice. For the past two decades, he has focused his studies on the threat of biological and chemical agents as a weapon of war. He has lectured and written numerous articles on infectious diseases and biological warfare.

Like anthrax, plague is a highly lethal bacterium. Unlike anthrax, plague is contagious - and poses a significant threat to America's national security.

Plague is present in many areas of the world and is endemic in prairie dogs and squirrels in the southwestern United States.

American scientists found that plague bacteria quickly lose infectivity in an aerosol. Weaponized plague was successfully developed after Pasechnik in the Soviet Union developed a powdered form covered with a polymer capsule.

The best delivery system, developed in Russia, is one that releases a canister that sprays a cloud of the dried and powdered bacterium from a low-flying and hard to detect object, the cruise missile.

Overview

Bubonic plague has been the most lethal disease pandemic (the term for an exceptionally widespread epidemic) in history. It killed one quarter of the European population in the 14th century. It is the most lethal, virulent and invasive disease known to man.

The plague bacterium, *Yersinia pestis*, is a rod-shaped bacillus that is non-motile (non-moving), doesn't form spores, stains red with Gram stain, and is of the family Enterobacteraceae.

It causes plague, a zoonotic disease (communicable from animals to humans) of rodents (e.g., rats, mice, ground squirrels and prairie dogs).

Various species of fleas that live on the rodents can transmit the bacteria to humans, who then suffer from the bubonic form of plague.

The bubonic form may progress to the septicemic (blood poisoning) and/or pneumonic forms.

Pneumonic plague is the most serious form of the disease and would be the predominant form after a purposeful aerosol dissemination.

Recovery from plague is followed by temporary immunity.

The organism remains viable in water, moist soil and grains for several weeks. At near freezing temperatures, it will remain alive from months to years but is killed by 15 minutes of exposure to 55°C.

It can live for some time in dry sputum, flea feces and buried bodies, but sunlight kills it within a few hours.

History and Significance

The United States worked with *Y. Pestis* as a potential biowarfare agent in the 1950s and 1960s before our offensive biowarfare program was terminated, and other countries are suspected of weaponizing this organism.

The former Soviet Union had more success than America and has tons of the dry powdered form for use as a bioweapon.

The Japanese army attempted to use infected fleas on the Chinese in World War II but met with little success. This method was cumbersome and unpredictable.

The Soviet Union developed the more reliable and effective method of aerosolizing the organism, and this method was later adopted in the U.S.

The contagious nature of pneumonic plague makes it particularly dangerous as a biological weapon.

Clinical Features

The three forms of plague in man are bubonic, septicemic and pneumonic.

Bubonic plague begins after an incubation period of two to 10 days, with high fever, malaise, headache, muscle aches and, usually, nausea, vomiting and diarrhea. Up to half of patients will have abdominal pain.

Simultaneous with or shortly after the onset of these nonspecific symptoms, the bubo develops - a swollen, tender lump or lymph node, usually noted in the groin, in the lymphatic drainage from the leg where a bite ordinarily occurs.

The liver and spleen are enlarged and tender. Twenty-five percent of victims will have a pustule, blister, dark scab, or pimple where the flea bite occurred.

Secondary septicemia (invasion of the bloodstream) is common, and 80 percent of patients will be positive for the bacteria on blood culture.

Occasionally the blood infection is primary, without buboes or skin lesions. The symptoms are similar to other Gram-negative septicemias: high fever, chills, malaise, hypotension, nausea, vomiting and diarrhea.

The blood may clot in the small vessels of the fingers and toes, with necrosis and gangrene; clotting may even occur throughout the vascular system.

Blackened distal extremities (fingertips) and purplish patches under the skin are caused by a toxin and are signs of impending death. The bacteria can also spread to the central nervous system, lungs and elsewhere.

Plague meningitis occurs in about 6 percent of septicemic and pneumonic cases.

Pneumonic plague is an infection of the lungs due to either inhalation of the organisms (primary pneumonic plague) or spread to the lungs from septicemia (secondary pneumonic plague).

The pneumonic form is by far the most serious and usually comes on two to four days after either inhalation or via the infected bloodstream.

The first signs of illness include high fever, chills, headache, malaise and muscle pain, followed within 24 hours by a cough with bloody sputum, which may contain visible pus. Gastrointestinal symptoms, including nausea, vomiting, diarrhea and abdominal pain, may be present.

Rarely, a bubo might be seen in the neck area from an inhalational exposure. The chest X-ray commonly reveals patchy pneumonia, although at times it may be consolidated (lobar). The pneumonia progresses rapidly, resulting in shortness of breath, crowing breath sounds, and blueness of the skin. The disease terminates in about 18 hours with respiratory failure and shock.

Nonspecific laboratory findings include a total WBC count up of to 20,000 cells with increased band cells, a sign of infection, and greater than 80 percent polymorphonuclear cells.

One also often finds increased fibrin split products in the blood, indicative of a low-grade onset of coagulation disorder. Signs of kidney and liver failure are usually evident in blood chemistry.

In the bubonic type, the death rate is about 60 percent, and close to 100 percent in the pneumonic type when treatment is begun beyond 18 hours after infection.

In the absence of biowarfare the pneumonic type is rare. In the U.S. over the past 50 years, four out of seven pneumonic plague patients (57 percent) died.

Diagnosis

Diagnosis is based primarily on clinical suspicion. The sudden appearance of large numbers of previously healthy patients with sudden onset of severe, rapidly progressive pneumonia with spitting up of blood strongly suggests plague. A blood smear, or examination of a bubo aspirate or spinal fluid, may demonstrate the organism. Blood culture is reliable and readily available, although studies of antibodies are specific when available.

The organism grows slowly at normal incubation temperatures, and may be misidentified by automated systems because of delayed biochemical reactions.

It may be cultured on blood agar, MacConkey agar or infusion broth. In immunoassay, a fourfold rise in antibody titer in patient serum is diagnostic, but the results tend to be available only after the patient is dead or has survived as a result of empiric treatment. Most clinical assays can be performed in Biosafety Level 2 labs, whereas procedures producing aerosols or yielding significant quantities of organisms require Level 3 containment.

Medical Management

Suspected pneumonic plague cases require strict isolation with masking and gowning to avoid droplets coughed by the patient.

Suspended droplets in the air around the patient are highly contagious. Isolation and quarantine must continue for at least the first 48 hours of antibiotic therapy, or until sputum cultures are negative in confirmed cases.

If competent vectors (fleas) and reservoirs (rodents) are present, flea insecticide sprays must be used, along with attempts at eradication of rodents near patient care areas.

In the areas of native infection, streptomycin, gentamicin, doxycycline, and chloramphenicol are highly effective, if begun early. The bioweaponized form from Russia is resistant to 16 different antibiotics and plague pneumonia is almost always fatal if treatment is not initiated with an effective antibiotic such as ciprofloxacin within 24 hours of the onset of symptoms.

Dosage regimens are as follows: gentamicin, 5mg/kg IM or IV once daily, or 2mg/kg loading dose followed by 1.75 mg/kg IM or IV every eight hours; doxycycline 200 mg initially, followed by 100 mg every 12 hours. Duration of therapy is 10 to 14 days. While the patient is typically afebrile after three days, the extra week of therapy prevents relapses. These may not be efficacious in resistant strains.. Recommended dosage of ciprofloxacin is 400mg IV twice daily. Chloramphenicol, 25 mg/kg IV loading dose followed by 15 mg/kg IV four times daily x 10-14 days, is required for the treatment of plague meningitis.

Usual supportive therapy includes IV saline and potassium if laboratory studies indicate. Monitoring of vital signs is important. Although low-grade coagulation disorders may occur, clinically significant hemorrhage is uncommon, as is the need to treat with heparin. Shock is common from the release of the bacterial endotoxin, but pressor agents such as dopamine are rarely needed. Buboes should not be drained, since they nearly always recede with antibiotic therapy and incision may tend to spread the infection to attendants. Aspiration with a needle and syringe is recommended for diagnostic purposes and may provide symptomatic relief.

Prophylaxis

Vaccine: No vaccine is available for prophylaxis of plague. A licensed, killed whole cell vaccine was available in the U.S. from 1946 until November 1998. It offered protection against bubonic plague, but was not effective against aerosolized *Y. Pestis*. A (fusion protein) antigen vaccine is in development at USAMRIID (U.S. Army Medical Research

Institute of Infectious Diseases). It protected mice for a year against an inhalational challenge and is being tested in primates.

Antibiotics: For face-to-face contacts (within 2 meters), patients with pneumonic plague or persons possibly exposed to a plague aerosol in a plague biowarfare attack should be given antibiotic prophylaxis using a quinolone such as ciprofloxacin for seven days or the duration of risk of exposure plus seven days. If fever or cough occurs in these individuals, treatment with IV antibiotics should be started.

Ciprofloxacin, 500 mg orally twice daily, has also shown to be effective in preventing disease if the patient does not have any symptoms of infection, and it may be more available in a wartime setting, as it is also distributed in blister packs for anthrax post-exposure prophylaxis.

Tetracycline, 500 mg orally four times daily, and chloramphenicol, 25 mg/kg orally four times daily, are acceptable alternatives if the strain is native and not genetically modified. Contacts of bubonic plague patients need only be observed for symptoms for a week. If symptoms occur, start treatment with antibiotics.

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