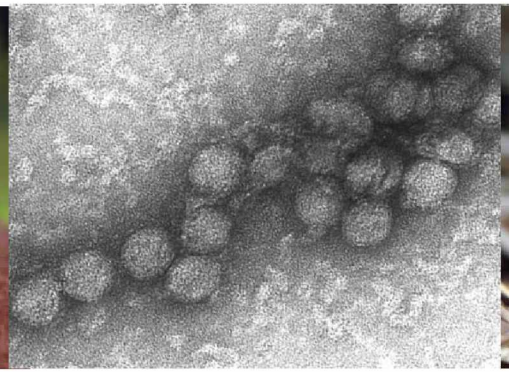
Back to the Future: Reflections on Recognition and Response to Emerging Infectious Diseases






James M Hughes, MD

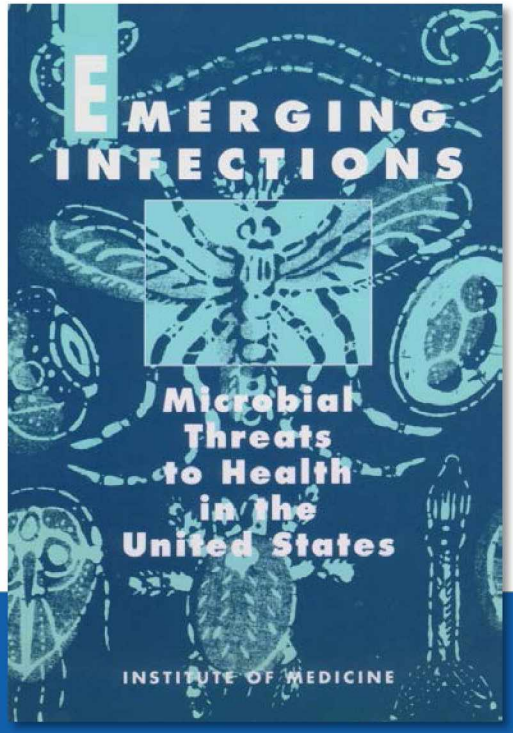
Professor of Medicine (Infectious Diseases) and Public Health (Global Health)

Emory University

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

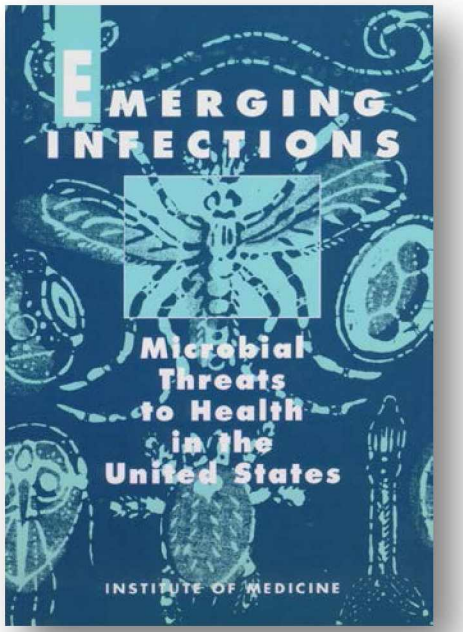
1992 Institute of Medicine Definition of Emerging Infections

New, reemerging or drug-resistant infections whose incidence in humans has increased within the past 2 decades or whose incidence threatens to increase in the near future



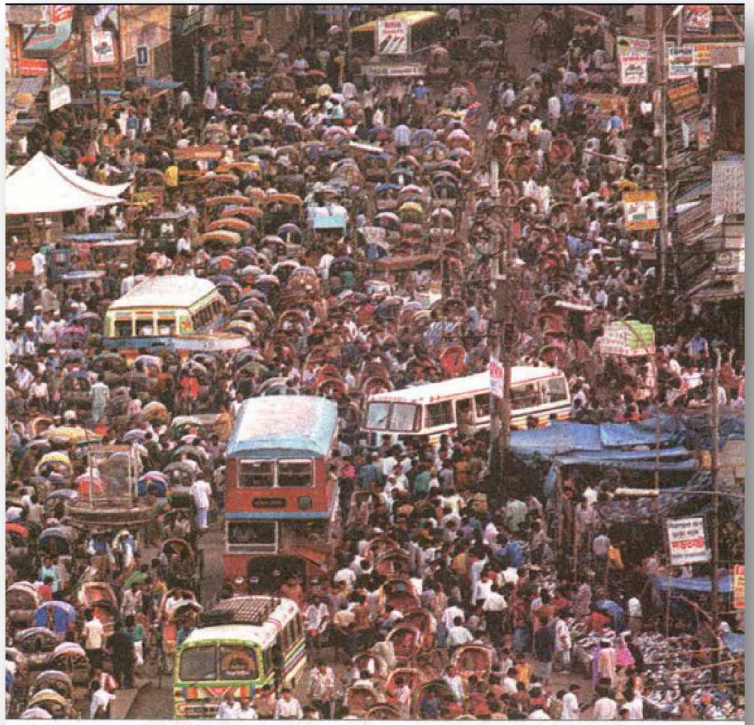
Factors Contributing to the Emergence of Infectious Diseases

- Human demographics and behavior
- Technology and industry
- Economic development and land use
- International travel and commerce
- Microbial adaptation and change
- Breakdown of public health measures



1992

Human Demographics and Behavior

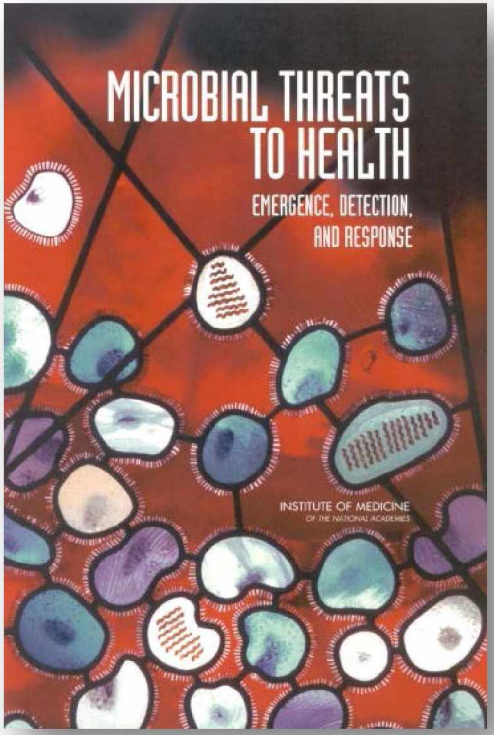


Associated P

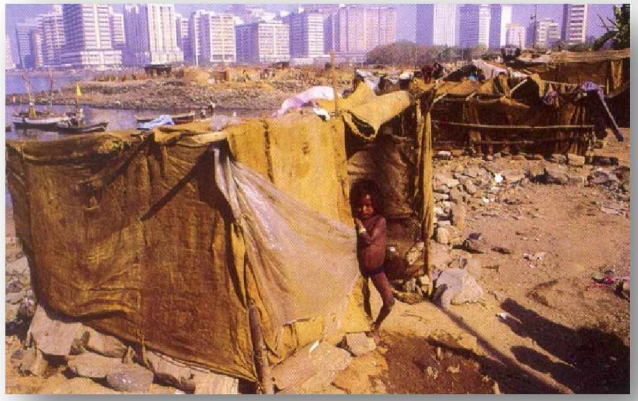
Bicycles, rickshaws, buses and pedestrians jam a street in Dkaha, Bangladesh.

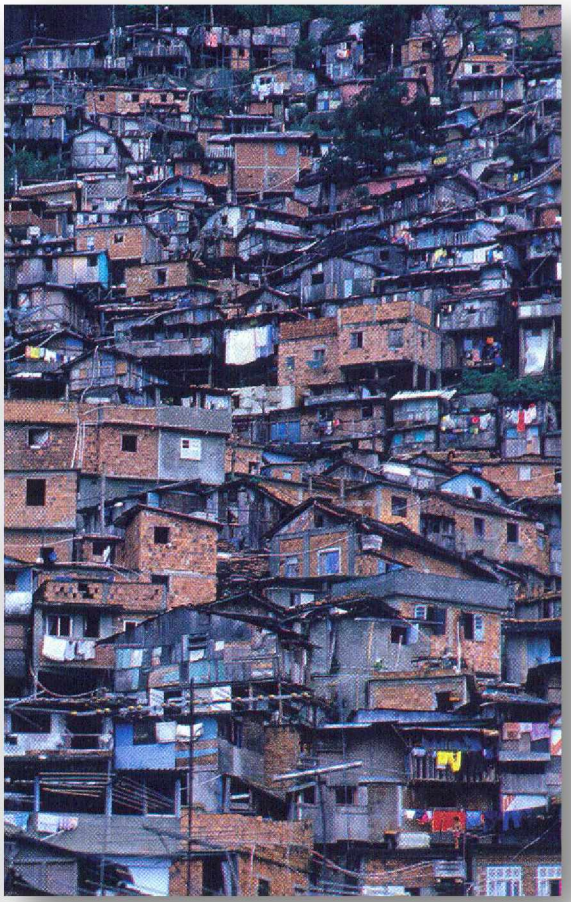
Additional Factors Contributing to the Emergence of Infectious Diseases

- Human susceptibility to infection
- Climate and weather
- Changing ecosystems
- Poverty and social inequality
- War and famine
- Lack of political will
- Intent to harm



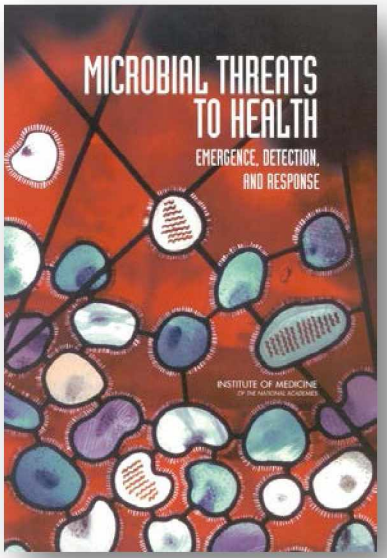
Poverty and Social Inequality





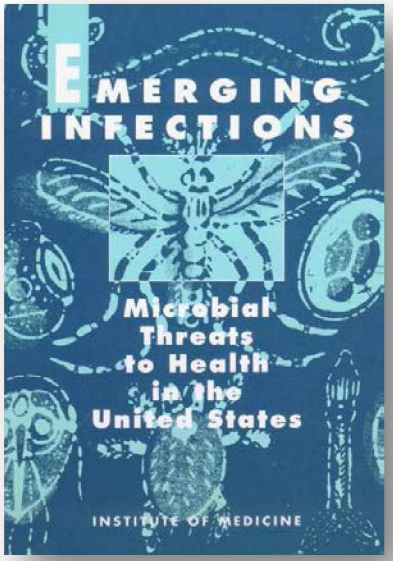
NEJM 2004; 350:1483; Lancet 2005;365:901-3

"A robust public health system—in its science, capacity, practice, and through its collaborations with clinical and veterinary medicine, academia, industry and other public and private partners—is the best defense against any microbial threat."



2003

Strategic Thinking and Program Priority Setting



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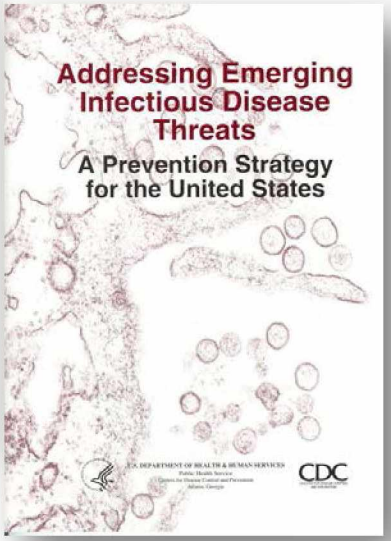
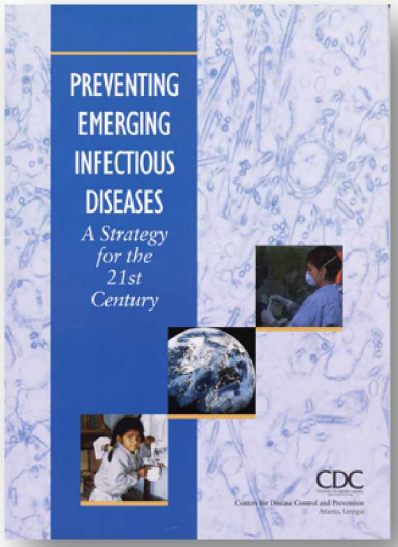
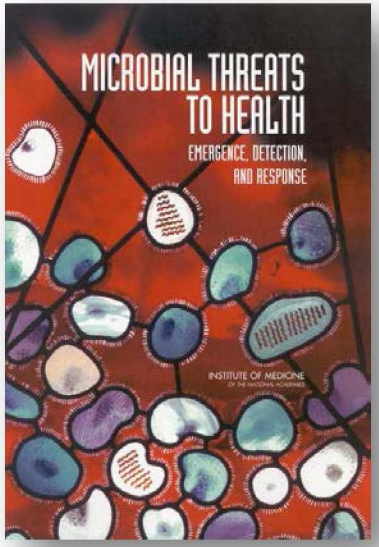


1994



1998



2003

A Decade of Global Infectious Disease Challenges

Year	Disease	Country
1993	Hantavirus pulmonary syndrome	United States
1994	Plague	India
1995	Ebola hemorrhagic fever Leptospirosis	Zaire Nicaragua
1996	New variant Creutzfeldt-Jakob disease	United Kingdom
1997	H5N1 influenza Vancomycin-intermediate S. *aureus*	Hong Kong Japan, United States
1998	Nipah virus encephalitis	Malaysia, Singapore

A Decade of Global Infectious Disease Challenges (cont.)

Year	Disease	Country
1999	West Nile encephalitis	Russia, United States
2000	Rift Valley fever Ebola hemorrhagic fever	Kenya, Saudi Arabia, Yemen Uganda
2001	Foot and mouth disease Anthrax	United Kingdom United States
2002	Vancomycin-resistant *S. aureus*	United States
2003	SARS Monkeypox	>25 countries Midwestern United States
2004	Avian Influenza (H5N1)	8 Asian countries

Zoonotic L

LEADING NEWSPAPER

ALBUQUERQUE JOURNAL

HOME-OWNED AND HOME-OPERATED

STATE

113th Year, No. 168 ■ 64 Pages In 5 Sections Thursday Morning, June 17, 1993 ■ Copyright© 1993, Journal Publishing Co. Daily 50¢ ■ Made in USA

Deer Mouse May Be Illness Culprit

DEER MICE POSSIBLE LINK TO MYSTERY ILLNESS

Deer mice, the rodents whose droppings may be linked to the Four Corners mystery illness, can live in a variety of regions of North America, ranging from mountain climates to swampy areas.

Sometimes known as white-footed mice, the deer mouse can range from 2 to 8 inches long. The fur on the upper parts of their bodies is gray with patches of white on the belly.

Reggie Fletcher, regional ecologist from the U.S. Forest Service, said deer mice can be found almost anywhere in New Mexico. They are most common in ponderosa pine regions, and also in northern sage grassland found in the Four Corners area.

"They will store grass seeds, flower heads and nuts in hollow logs," Fletcher said. "They will store what's available and what they can carry." Fletcher said the deer mouse is a key indication of diversity in the ecosystem, since the rodent is a major prey base for larger animals.

Tests Show Rodent Is Likely Carrier

By Rex Graham

JOURNAL STAFF WRITER

In a major breakthrough, test results point to the lowly deer mouse as the possible carrier for spreading the Four Corners mystery illness that's killed at least 16 people.

A preliminary report to be released Friday by the federal Centers for Disease Control and Prevention says 12 deer mice trapped in and near the homes of some of the mystery illness' victims tested positive for exposure to a Hantavirus.

Hantaviruses are known to be carried by rodents, but never to have caused the kind of severe respiratory disease that recently struck about 36 people in New Mexico, Arizona, Colorado and Utah.

The report says 42 rodents of different types were tested, and 12 of them turned up positive for exposure to a Hantavirus. "All 12 were of the species Peromyscus maniculatus (deer mouse)," said the report.

A copy of the report obtained by the Journal also gives another strong piece of evidence that links what researchers think is a new type of Hantavirus with the illness. Hantavirus genetic material was isolated from the tissues of two patients who died recently from the disease.

The findings were made possible by a sophisticated new test called a polymerase chain reaction that can detect tiny amounts of viral genetic material in diseased tissue. Officials also credit unprecedented cooperation between dozens of state and federal health experts for eliminating other possible causes of the epidemic.

For state health workers, many of whom have put in 16-hour days for a month, the CDC report is a watershed.

"We're ecstatic," Dr. Gary Simpson, medical director of infectious diseases for the New Mexico Department of Health, said in a telephone interview Wednesday. "We've come so far so quickly. All of us are tired. A lot of us are very close to patients' families and have a lot of pain for them."

The tests did not confirm that the same Hantavirus was responsible for infecting both the mice and people. That association will be proved or disproved in the coming weeks.

The report also does not shed light on how people were infected.

"That's the piece that's still unknown. We still have that piece to figure out," said Dr. Norton Kelly-Hope, chief medical officer for the state Department of Health.

Experts assume the victims

(CONT. from CLASSES on PAGE A2)

■ Navajos face health issue

From China's Provinces, a Crafty Germ Breaks Out

Justin Guariglia/Contact, for The New York Times

Workers prepared wild game hens on the floor of a restaurant in Guangzhou, China. Food workers were among the earliest SARS patients.

inkages

Anthrax

Is That an Epidemic — or a Terrorist Attack?

Bioterrorism Is the Least of Our Worries

DIALOGUE

A Lethal Weapon We Must Learn to Recognize

By Jonathan B. Tucker

The news media are fascinated with bioterrorism. After a New Yorker article this week quoted unnamed Central Intelligence Agency analysts who speculated, apparently wrongly, that the outbreak of West Nile-like fever in New York could have been the work of Iraqi terrorists, a number of television news programs reported the story. And earlier this month, ABC's "Nightline" aired a weeklong docudrama in which a hypothetical anthrax attack on the subway system of a major city inflicts more than 50,000 deaths.

This sort of worst-case scenario is extremely unlikely. In truth, most terrorists aren't interested in staging catastrophic biological attacks, and those who are would have significant technical hurdles to overcome.

Over the past century, not a single provide technical help, but only at grave risk: the sponsor could lose control over the terrorists and invite severe retaliation if its involvement became known. Or a wealthy terrorist group might try to recruit scientists formerly employed by the Soviet Union, for example, which had advanced bioweapons programs. But no evidence currently available points to such assistance.

Without technical help, small terrorist cells would have a hard time mounting a large-scale biological attack. Germs suitable for warfare are difficult to mass-produce and even harder to disseminate effectively. Microbes might be spread, for example, as an aerosol cloud, but it is technically complex and dangerous to produce a concentrated aerosol that could infect thousands of people. Contaminating urban water supplies is also beyond the ability of most terrorists, mainly because a huge volume of harmful agent would be needed to overcome the effects of dilution, chlorination and filtration.

In the late 1980's in Japan, the Aum Shinrikyo cult, which had vast financial resources, recruited scientists from leading Japanese universities to develop bioweapons. But even though the cult acquired anthrax bacteria and botulinum toxin and carried out several attacks in Japan, no injuries or deaths were reported. The cult then resorted to sarin, a chemical nerve agent. In March 1995, the group released the poison on the Tokyo subway, killing 12 people and injuring more than a thousand.

Given the constraints, a bioterrorist attack in the United States in which thousands of people are killed remains extremely unlikely. While planning for such an event is warranted, government authorities should pay attention to a far more probable scenario: small-scale incidents involving food or drug contamination, which could cause widespread fear and economic disruption. □

By Jessica Stern

CAMBRIDGE, MASS.

The flurry of rumors last week about the origins of the encephalitis outbreak in the New York metropolitan area proved how anxious we are about biological terrorism.

After an article in The New Yorker quoted unnamed Central Intelligence Agency sources who speculated that the West Nile-like virus might have been spread in an Iraqi biological attack, the C.I.A. found itself having to reassure the public that this chain of events was highly unlikely.

And indeed, it is.

For one thing, West Nile encephalitis is a relatively mild disease, and Saddam Hussein has far more virulent agents in his arsenal. For another, the outbreak has all the earmarks of a naturally occurring infectious disease, according to the Centers for Disease Control and Prevention.

But this case illustrates one of the most troubling aspects of biological terrorism: it can be extremely difficult to distinguish germ warfare from a natural outbreak of disease.

After all, this is not the first time that biological attacks have been blamed for sudden epidemics. In 1997, when foot-and-mouth disease struck pigs in Taiwan for the first time in 83 years, the Taiwanese Government was forced to slaughter some four million hogs. Taiwanese farmers, without any evidence, suspected that China had deliberately introduced the disease on the island to damage the economy.

After Cuba suffered an epidemic of dengue fever in 1981, it accused the United States of biological aggression. In 1997 Cuba made a similar claim, charging that the United States had dropped crop-eating pests from a low-flying plane.

On the rare occasions when biological weapons have been used or accidentally released, scientists and government officials often first assumed that the epidemics were natural outbreaks.

> Our uncertainty about a virus's origin is a warning.

For instance, many American security experts initially believed that a 1979 outbreak of anthrax in the Soviet Union was caused by contam-

Jessica Stern, a fellow at Harvard's Center for Science and International Affairs, is the author of "The Ultimate Terrorist."

2001

Anthrax Found in NBC News Aide

Suspicious Letter Is Tested at Times — Wide Anxiety

By DAVID BARSTOW

An assistant to the NBC anchor Tom Brokaw has tested positive for anthrax infection more than two weeks after she opened a threatening letter addressed to Mr. Brokaw that contained a white powder, officials said yesterday.

Even as law enforcement officials were cordoning off Rockefeller Center, the newsroom at The New York Times was evacuated when a reporter opened an envelope that also contained a white powder.

The substance was still being tested last night, as investigators explored potential links between the two incidents. Both letters were mailed from St. Petersburg, Fla., and had similar handwriting, according to law enforcement officials.

The reports of possible bioterrorism caused widespread anxiety in New York and across the country. People depleted supplies of antibiotics at drugstores and besieged their doctors. Offices were evacuated after a spate of threats, and companies made emergency adjustments to the way they received mail. [Page B9.]

The NBC case marked the second time an American has been stricken with a form of anthrax since the Sept. 11 terror attacks.

In the other case, a man died after he contracted an inhaled form of the disease at a newspaper office in Boca Raton, Fla. Two other people at the office were exposed to anthrax

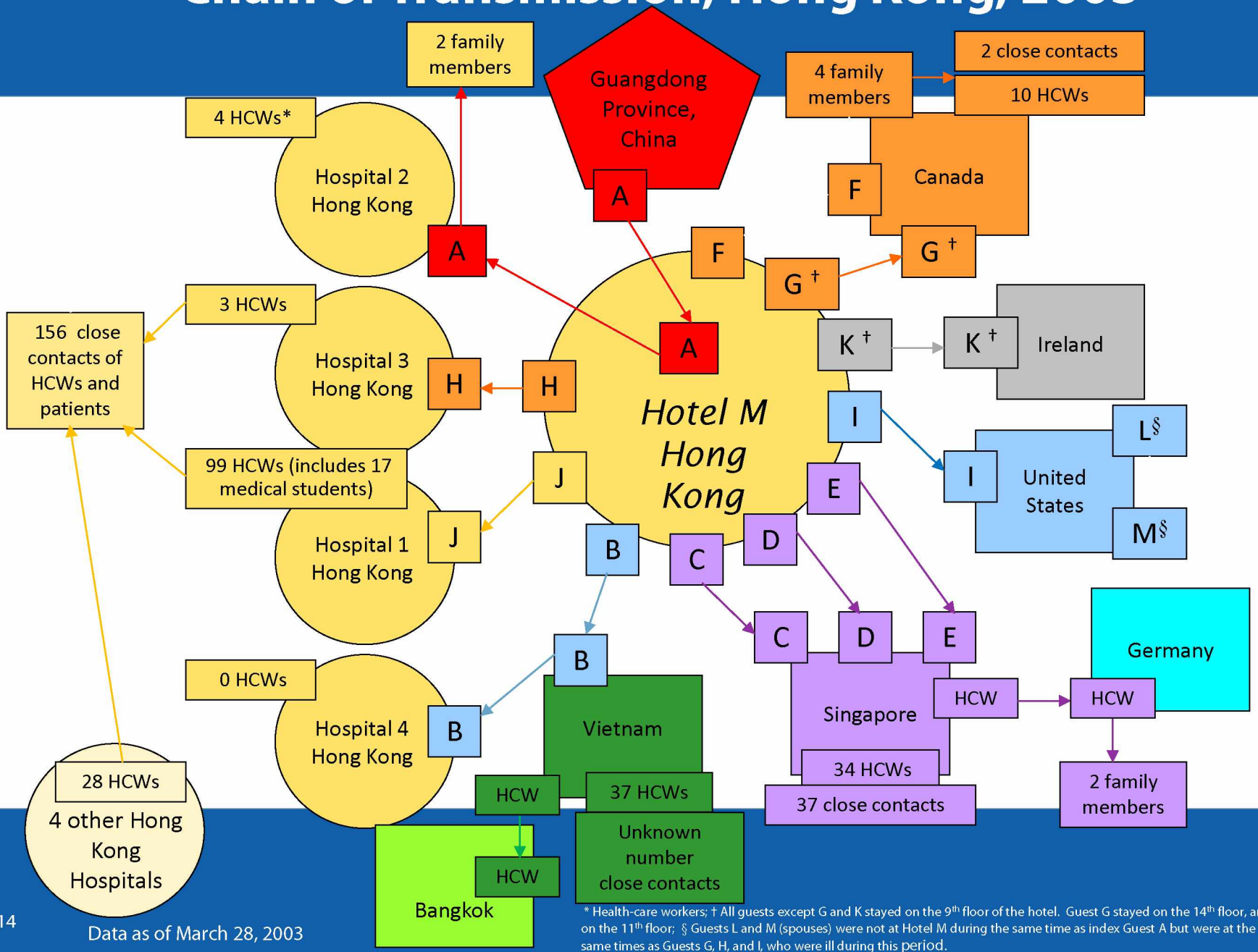
Reuters

Mayor Rudolph W. Giuliani after a news conference yesterday at NBC, where he tried to calm new fears that were raised by an anthrax case.

Recognition of Anthrax in New York City

- **38 year old woman; NBC TV anchor assistant**
- **Recalled handling a suspicious letter with powder before onset**
- **Cutaneous lesion onset 9/25/01**
  - Central necrosis with eschar
  - Cultures negative
  - Immunohistochemical staining of skin biopsy at CDC showed *B. anthracis* on 10/12/2001

Chain of Transmission, Hong Kong, 2003



* Health-care workers; † All guests except G and K stayed on the 9th floor of the hotel. Guest G stayed on the 14th floor, and Guest K stayed on the 11th floor; § Guests L and M (spouses) were not at Hotel M during the same time as index Guest A but were at the hotel during the same times as Guests G, H, and I, who were ill during this period.

Data as of March 28, 2003

The Importance of State of the Art Molecular Methods

INFECTIOUS DISEASE

Molecular Methods Fire Up the Hunt for Emerging Pathogens

Combining an early warning system with genetic techniques, microbiologists have stepped up the hunt for emerging pathogens in the United States

When a 3-year-old Connecticut girl was hospitalized with an often-fatal type of kidney failure last year, doctors at first suspected that she was infected with *Escherichia coli* O157:H7, a dangerous strain of bacteria that can cause kidney failure in children. But all attempts to culture this and other pathogens failed. Fortunately, the girl recovered, and the case became one of the thousands of unexplained illnesses put on the books every year in the United States.

This time, however, the story didn't end there. To track down the mystery pathogen, doctors turned over samples of the girl's blood taken during the height of her illness to a specialized pathogen lab in California, via the Unexplained Illness Working Group, a network of infectious-disease experts coordinated by the Centers for Disease Control and Prevention (CDC) in Atlanta. The California lab used sensitive molecular and immunological probes to identify the pathogen: an unknown strain of enterovirus, a large group of microbes that includes the poliovirus. This information came too late to help the Connecticut girl, but researchers are still probing the virus's genome to see if it matches one of the more than 70 known enterovirus strains, or if it is a new pathogen.

This is just one example of how new molecular technologies are speeding the hunt for microbes that have recently begun to attack human hosts, or so-called emerging pathogens. To fight these bugs, researchers are now going beyond the traditional means of identifying pathogens—culturing them in petri dishes and test tubes—and isolating the DNA or RNA that makes up their genomes. The enterovirus that infected the Connecticut girl, for example, was spotted by matching a segment of its RNA to that of other known enteroviruses. The Unexplained Illness Working Group, created by the CDC in 1994, is one leader in this effort, focusing not on the tropics, home to infamous viruses such as Ebola, but on the familiar settings of U.S. hospitals and clinics, where new and deadly strains may also emerge.

CREDIT: CDC

Pathogen central. The CDC in Atlanta is at the hub of a microbe-spotting network.

The network serves as an early warning system for dangerous microbes as well as a focal point for research on new tests. And over the past year the team has revved up to full speed: Some 200 cases of unexplained illness are under active investigation, and results are starting to emerge. The network has tracked down possible new strains of enterovirus—implicated in a number of recent outbreaks of childhood disease in the United States and Asia—and has uncovered evidence that microbes once thought innocuous can cause disease. For example, the team has found that human herpesvirus 6, previously thought to be benign when it infects children, is behind some cases of childhood encephalitis. Once new pathogens have been identified, says CDC epidemiologist Bradley Perkins, the working group's Atlanta-based coordinator, the ultimate goal is to develop a "diagnostic test that a clinician could order in the hospital."

The evidence so far suggests that some unidentified killers may already be out there. In up to 14% of deaths caused by infection in people between the ages of 1 and 49, no known microbe could be identified as the culprit, according to surveys carried out over the past few years by the working group and other collaborators.

But finding these silent killers isn't easy. The time-honored means of identifying an invading microbe is by taking blood and tissue samples and trying to culture the organism in various artificial growth media, then identifying it either under the microscope or with

SCIENCE 1998; 282:219

Examples of Advanced Molecular Detection Techniques

Nucleic acids

- Polymerase chain reaction (PCR)
- Real time reverse transcription PCR
- Genome sequencing
- Pulsed field gel electrophoresis (PFGE)
- Multilocus VNTR analysis (MLVA)
- Spoligotypying

Proteins

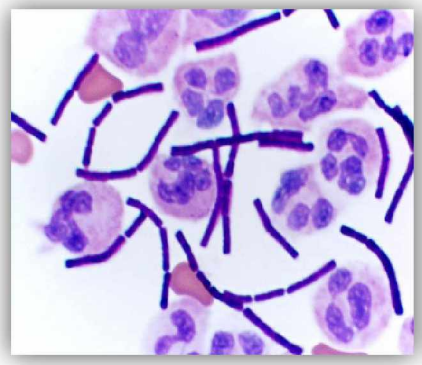
- Crystallography: Protein structure and protein-protein interactions
- Ag–Ab complex rapid detection methods
- Immunohistochemistry (IHC): Agent identification within tissues
- Direct and indirect fluorescent assays
- IgM antibody capture ELISA (MAC-ELISA)

Other

- Nanotechnology: Imaging, etc,
- Microarrays/gene chip methodologies: Large scale biological agent or antibody screening
- Mass spectrometry techniques: Chemical composition/structure of molecules
- Genetic engineering
- Electron microscopy
- Phylogenetic analysis: Compare and contrast the relatedness of gene sequences

Vigilance

- The "Alert" Physician
- The "Alert" Veterinarian
- The "Alert" Pathologist / Laboratorian
- The "Alert" Research Scientist
- The "Alert" Public Health Official



Transplants led to rabies deaths

3 cases traced to lone donor could prompt new screening

By DAVID WAHLBERG
dwahlberg@ajc.com

Three people died from rabies after receiving organs from a donor later found to have had the disease — the first reported cases of rabies spread through organ transplants, health officials said Thursday.

Federal officials say they will review whether more screening is necessary. Transplant agencies currently test organs for HIV, hepatitis and other viruses, but not for rabies, though some agencies ask if potential donors were exposed to possibly rabid animals.

"We are learning as we go," said Dr. Mitchell Cohen, an infectious disease expert with the Centers for Disease Control and Prevention. "This has never happened before."

The organ recipients, from Texas and Oklahoma, received a liver and two kidneys on May 4 at Baylor University Medical Center in Dallas. The donor, a 20-year-old Arkansas man, had died the previous day at Christus St. Michael Health System in Texarkana, Texas, hospital spokeswoman Francine Francis said.

The donor had gone to the Texarkana hospital April 28 for treatment of nausea and vomiting, Francis said.

He developed "severe mental status changes" and was diagnosed with a brain hemorrhage, Cohen said.

The transplant patients died from rabies June 7-21, Cohen said. A fourth patient, who received two lungs from the donor, died from surgical complications during the transplant at the University of Alabama, Birmingham.

The CDC and health officials from Alabama, Arkansas, Oklahoma and Texas are checking whether health care workers, family members or friends who had close contact with the donor or four recipients should get rabies treatment — a dose of immune globulin followed by five shots of rabies vaccine over 28 days.

Rabies may be transmitted between people through saliva, though Cohen said only two such cases have been reported, both in Ethiopia. They were not confirmed by lab tests.

It usually takes one to three months before people infected with rabies show symptoms, but it can take years, the CDC said. It is not known how the organ donor from Arkansas contracted the virus, but the strain found in all of the patients suggests it came from a bat, Cohen said.

People with rabies generally develop fever and headache, followed by confusion, hallucinations and insomnia. The disease is nearly always fatal. The United States sees one to three human cases a year, usually caused by bites or scratches from bats.

Though rabies has never been known to be passed through organ transplants before, at least eight people have contracted the virus worldwide through corneas transplants, the CDC says.

Organs in America are tested for HIV, hepatitis B and C, syphilis and two other viruses, cytomegalovirus (CMV) and human T-lymphotropic virus (HTLV), said Virginia McBride, an organ donation specialist with the U.S. Health Resources and Services Administration. Organs from five donors are now also tested for West Nile virus — which was transmitted from a Georgia organ donor two years ago to four recipients, one of whom died.

Cohen said health officials will now consider testing organs for rabies. Since the virus travels in nerves, and not blood, there is no danger of spreading rabies through blood transfusions, he said. In the transplant patients who died, he said the virus probably lingered in the nerves of the organs.

While the rabies cases are cause for concern, nearly all of the 25,000 organ transplants in the country each year are safe, said Dr. Daniel Hayes of the United Network for Organ Sharing.

"I don't think that such a rare event should trigger any kind of widespread panic or testing on a disease that is so infrequent," he said.

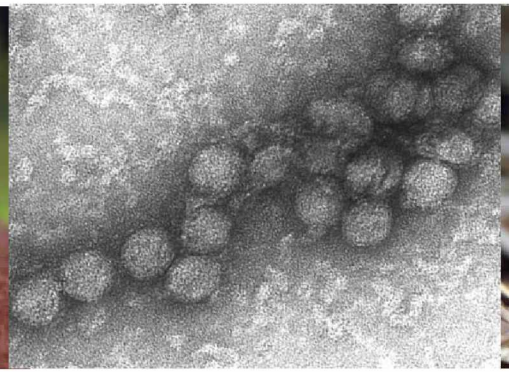
Public Health Dispatch

West Nile Virus Infection in Organ Donor and Transplant Recipients — Georgia and Florida, 2002

On August 23, 2002, the Georgia Division of Public Health (GDPH) and CDC were notified of two cases of unexplained fever and encephalitis in recipients of organ transplants from

The Exciting World of a CDC Pathologist!






Sherif R Zaki, MD, PhD
Infectious Diseases Pathology Branch
Centers for Disease Control and Prevention

Infectious Disease Pathology and Public Health

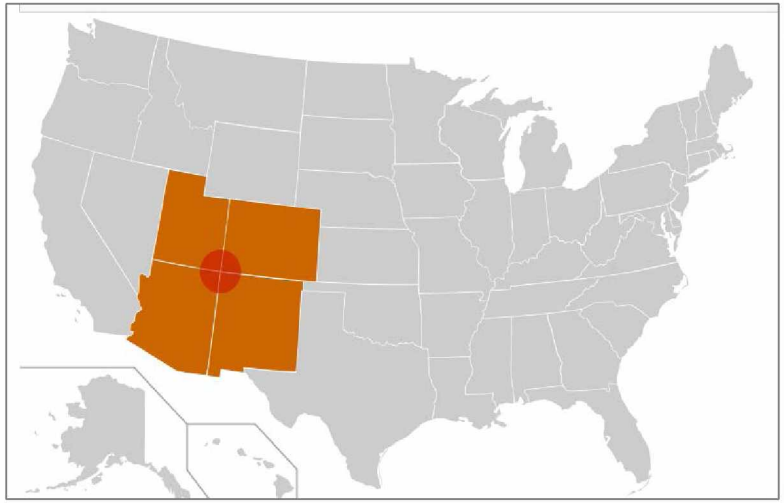
- **Pathologists are among first to encounter infectious disease outbreaks and are in excellent position to discover emerging infectious diseases**
- **Collaborative research with**
  - Epidemiologists, clinicians, veterinarians, microbiologists
- **Many examples of recent emerging infectious diseases have been diagnosed through autopsies which are increasingly being viewed as effective surveillance tools**

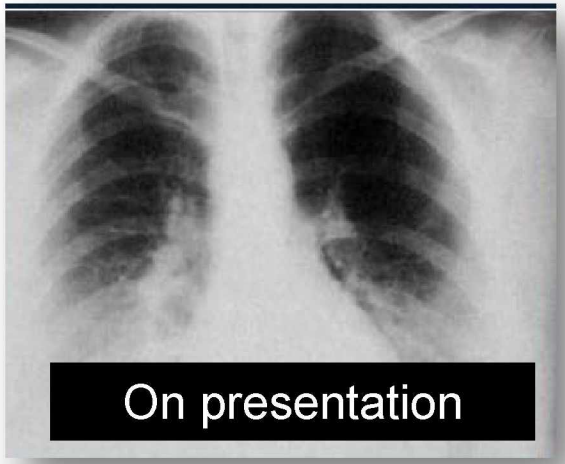
Our Approach to Diagnosis

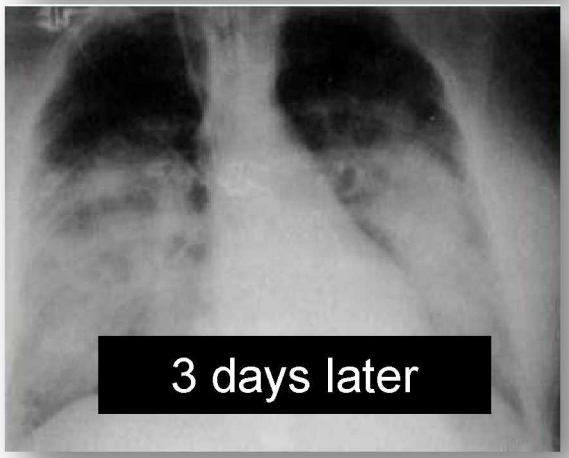
- **Histopathologic pattern**
- **Clinical and epidemiologic features**
- **Multi-disciplinary laboratory approach**
  - Culture
  - Serology
  - Electron microscopy (EM)
  - Immunohistochemistry (IHC)
  - Molecular technologies

Unexplained Respiratory Illness: May 1993

- Previously healthy young adults
- Influenza-like illness
- High mortality
- Massive pleural effusions







Unexplained Respiratory Illness: May 1993
Many Theories, but No Real Fit

NEW MEXICO'S LEADING NEWSPAPER

ALBUQUERQUE JOURNAL

HOME-OWNED AND HOME-OPERATED

113th Year, No. 151 ■ 66 Pages In 4 Sections — Monday Morning, May 31, 1993 ■ Copyright© 1993, Journal Publishing Co. — Daily 50¢ ■ Made in USA

Desert Mystery: Death Toll at 10

"We have not been able to identify any place where people have gone or any gathering in common. Nothing really fits ..."
– Dr. Ron Voorhees

It's an Epidemic, But 'Nothing Fits'

Sickness, Toxin May Be Acting Together

How Scientists Are Searching For the Cause

Here are some of the types of microbiological tests being used:

Tests being performed at the **Centers for Disease Control and Prevention** in Atlanta

LAB ANIMAL TESTING

Tests being performed at the state **Scientific Laboratory Division** in Albuquerque

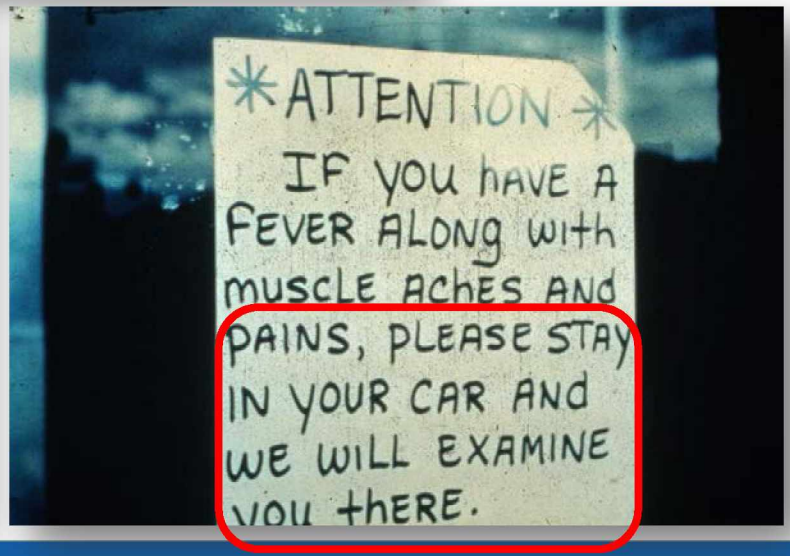
Illness May Not Be 'Highly Contagious,' State Doctor Says

Secret CIA files reveal ...

GERM WARFARE TEST ACCIDENT KILLED NAVAJO INDIANS

THE MYSTERY disease ravaging Indians in the Southwest was triggered by a vicious germ warfare virus captured from Iraq during the Gulf War — and unleashed by the CIA!

An EXAMINER probe has exposed shocking evidence that the Central Intelligence Agency secretly spread the virus through Indian reservations to test its potency and

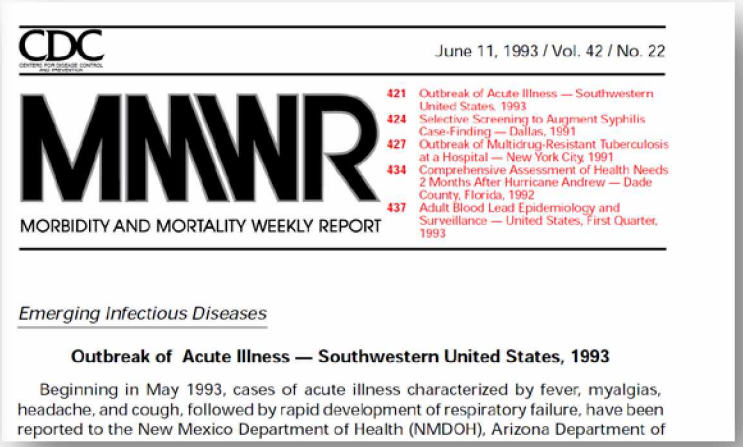


Hantaviral Antibodies Detected in Patients' Sera But There Was Skepticism

- **Serology testing at CDC Special Pathogens Branch showed indication that hantavirus may be the culprit**

NEW MEXICO LAST ELISA NEWS JUNE 4,1993

	HANTAAN		PUUMALA		SEOUL	
Serum #	IgG	IgM	IgG	IgM	IgG	IgM
1121	-	-	-	100	100	400
1122	100	-	1600	-	400	-
1125	-	-	-	-	-	-
1129	-	-	-	1600	400	1600
1134	-	-	-	-	-	-
1148	-	-	-	-	-	-
1154	-	1600	-	1600	-	6400



CDC

June 11, 1993 / Vol. 42 / No. 22

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Emerging Infectious Diseases

Outbreak of Acute Illness — Southwestern United States, 1993

Beginning in May 1993, cases of acute illness characterized by fever, myalgias, headache, and cough, followed by rapid development of respiratory failure, have been reported to the New Mexico Department of Health (NMDOH), Arizona Department of

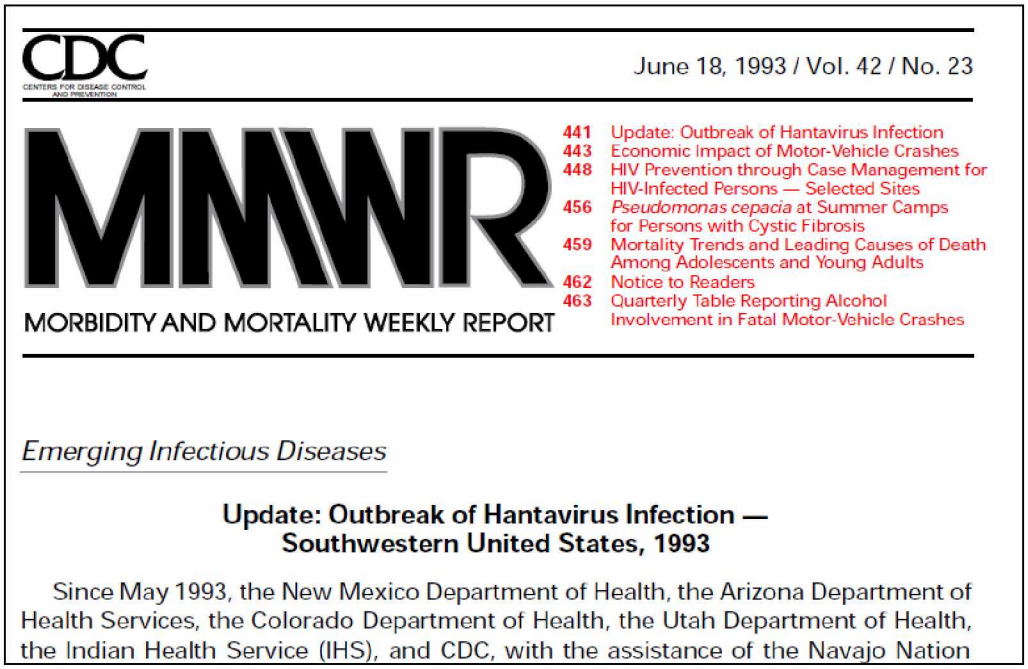
What We Know about Hantaviruses in 1993

- **Clinical presentation**
  - Hemorrhagic renal (*not pulmonary*) syndrome
- **Geographic distribution**
  - No pathogenic forms of hantaviruses were known to exist in North America

Distribution of hantavirus associated diseases before 1993

What We Did in 1993

Novel Immunohistochemistry and PCR tests at CDC helped identify the emerging hantavirus



CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

June 18, 1993 / Vol. 42 / No. 23

MMWR
MORBIDITY AND MORTALITY WEEKLY REPORT

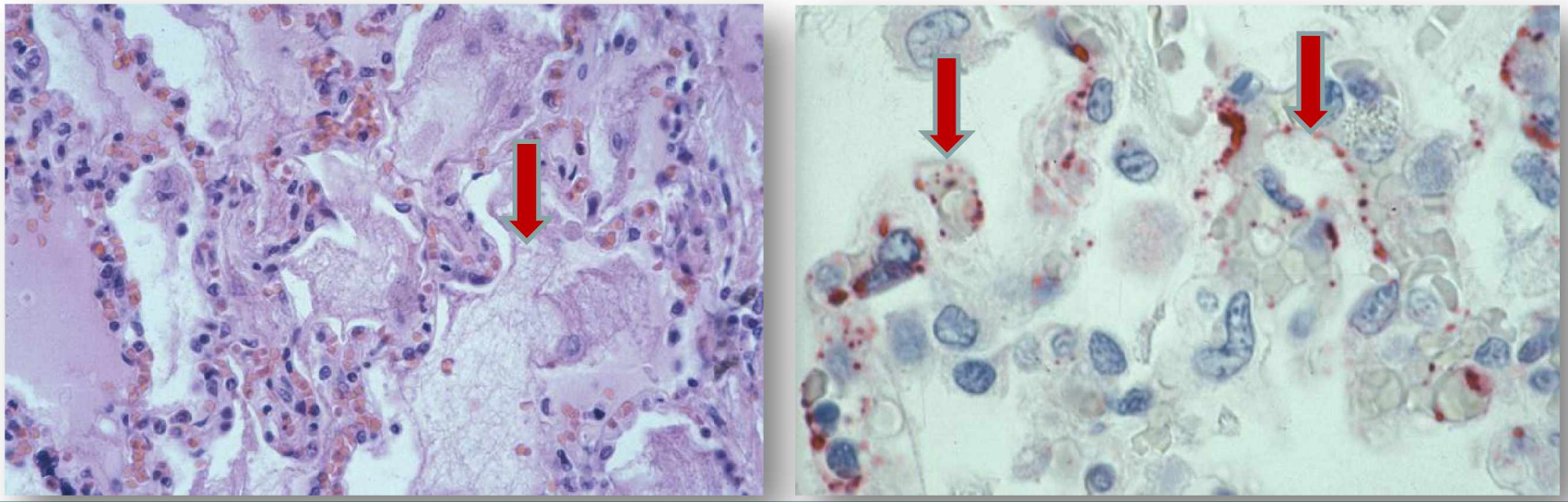
Emerging Infectious Diseases

Update: Outbreak of Hantavirus Infection — Southwestern United States, 1993

Since May 1993, the New Mexico Department of Health, the Arizona Department of Health Services, the Colorado Department of Health, the Utah Department of Health, the Indian Health Service (IHS), and CDC, with the assistance of the Navajo Nation

Immunohistochemistry (IHC)

- Localizes target pathogen proteins in tissues
- Hantaviral IHC assay used a monoclonal antibody that cross-reacted with all hantaviruses
- Localized viral proteins to lung and small blood vessels (capillary leak)

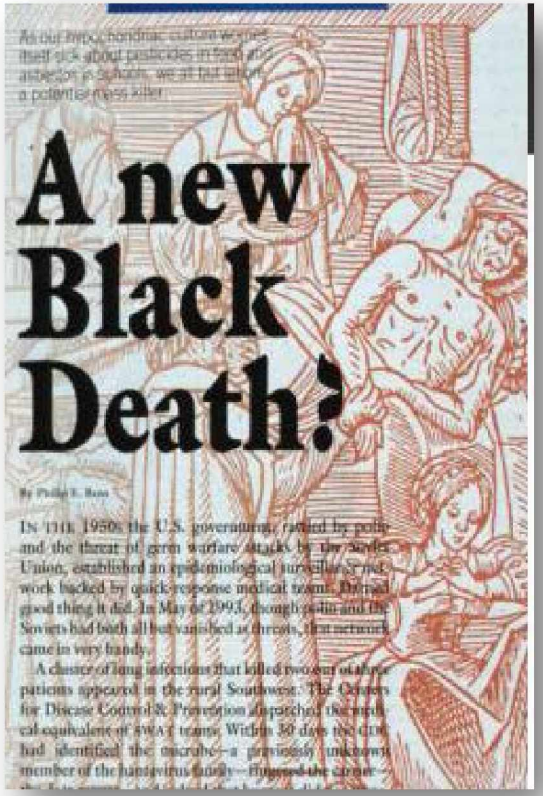


Photomicrographs of lungs: Pulmonary edema (L) and viral proteins (R)

Polymerase Chain Reaction (PCR) of Virus Sequences in Tissues

Targeting a conserved area of M segment that encodes viral glycoproteins sequencing identified a novel hantavirus (Sin Nombre Virus)

How Our Discoveries Helped Move the Field Backwards



A new Black Death?

By Phillip E. Bass

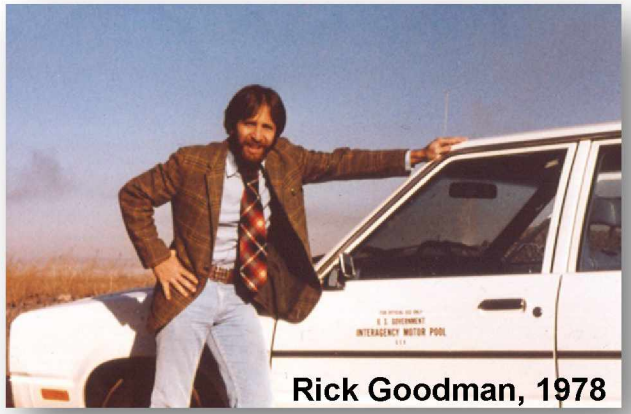
In 1111, 1950s the U.S. government, rattled by polio and the threat of germ warfare attacks by the Soviet Union, established an epidemiological surveillance network backed by quick-response medical teams. Did it good thing it did. In May of 1993, though polio and the Soviets had both all but vanished as threats, that network came in very handy.

A cluster of lung infections that killed two out of three patients appeared in the rural Southwest. The Centers for Disease Control & Prevention dispatched the medical equivalent of SWAT teams. Within 30 days the CDC had identified the microbe—a previously unknown member of the hantavirus family—[illegible] the carrier—

Retrospective Diagnosis of Hantavirus Pulmonary Syndrome, 1978–1993

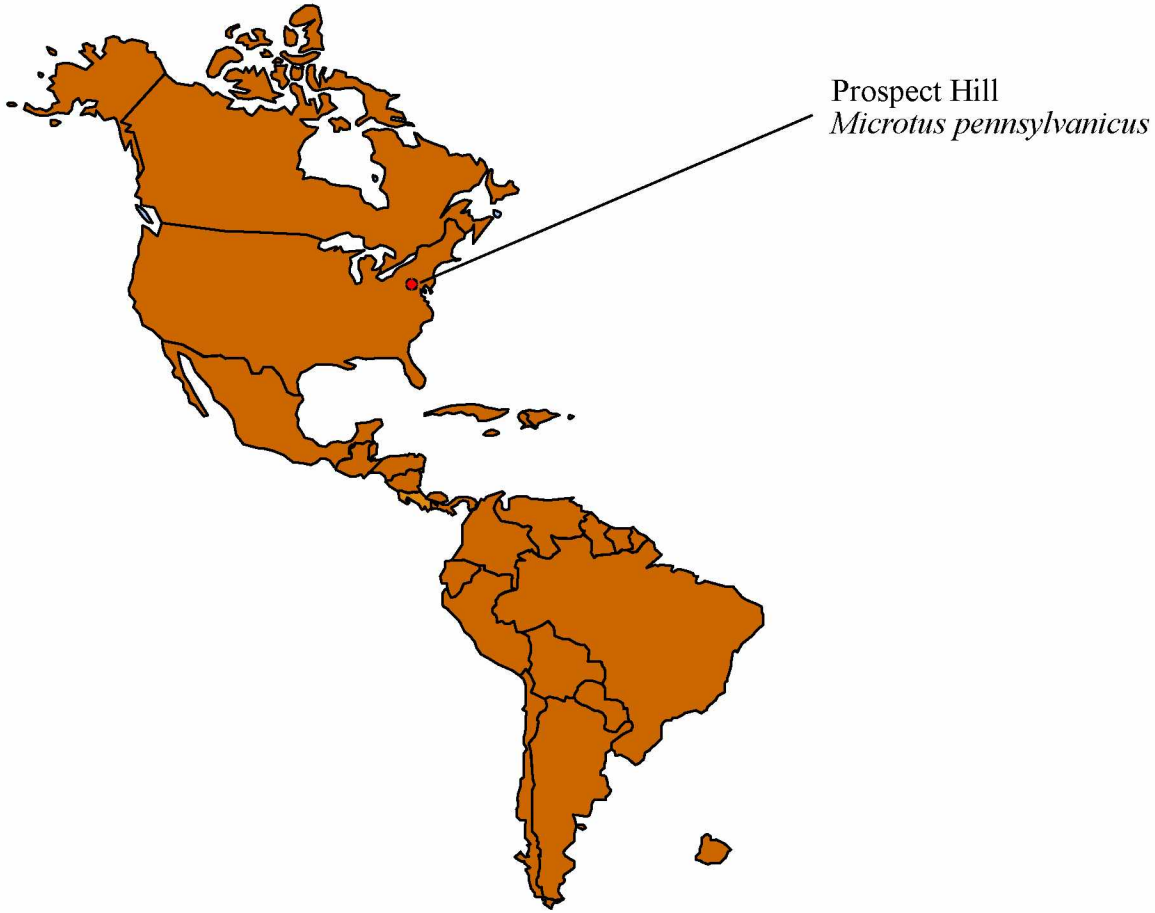
Implications for Emerging Infectious Diseases

Sherif R. Zaki, MD, PhD; Ali S. Khan, MD; Richard A. Goodman, MD; Lori R. Armstrong, PhD; Patricia W. Greer; Lisa M. Coffield; Thomas G. Ksiazek, DVM, PhD; Pierre E. Rollin, MD; C. J. Peters, MD; Rima F. Khabbaz, MD



Arch Pathol Lab Med. 1996;120:134-139

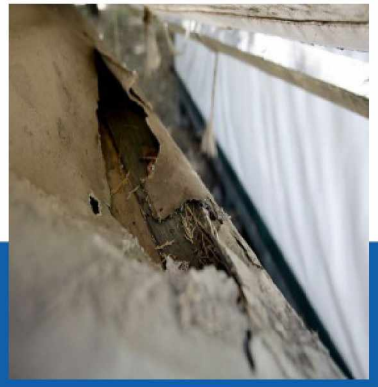
New World Hantaviruses 1993



New World Hantaviruses 2012

Today: Hantavirus Pulmonary Syndrome (HPS)

- **Investigation in the Yosemite National Park (YNP)**
  - As of September 18, 2012: 9 confirmed cases and 3 deaths associated with staying at YNP
- **Better understanding of HPS is critical for**
  - Fast recognition of illness
  - Better clinical management
  - Better understanding of natural reservoir (rodents), mode of transmission and consequently impact on control, prevention, and community outreach measures



Mystery Illness in Nicaragua, 1995

- **Respiratory illness**
  - Rapid progression of pulmonary hemorrhage
- **Hundreds affected with many deaths**
- **Virus suspected**

Mystery virus hits Nicaraguan towns

Hundreds stricken; 11 dead so far

By John Otis
SPECIAL TO THE WASHINGTON TIMES

ACHUAPA, Nicaragua — In just four days, Ines Galeano Hernandez became an emergency foster parent when his neighbor began hemorrhaging and went into shock.

"On Monday, she caught a fever. On Wednesday, they took her to the hospital. By dawn on Thursday, she was dead," Mr. Galeano said as he and his wife cuddled the crying infant daughter the dead woman left behind.

A devastating virus, which doctors have been unable to identify, is sweeping through Achuapa and other villages in northern Nicaragua. It has infected more than 600 people in the past two weeks. At least 11 have died from internal bleeding and shock.

Feverish and dehydrated patients, many of whom must be carried down from the mountains in hammocks or on horseback, crowd into the tiny health center in Achuapa each day.

Doctors and nurses from Managua, the capital, have been airlifted to the clinic, where patients lie sweating on cots with IVs dripping saline solution into their arms. Some are doused in cold water to bring down the fever.

"You get a fever, headache and chills. It's very terrible. It feels like

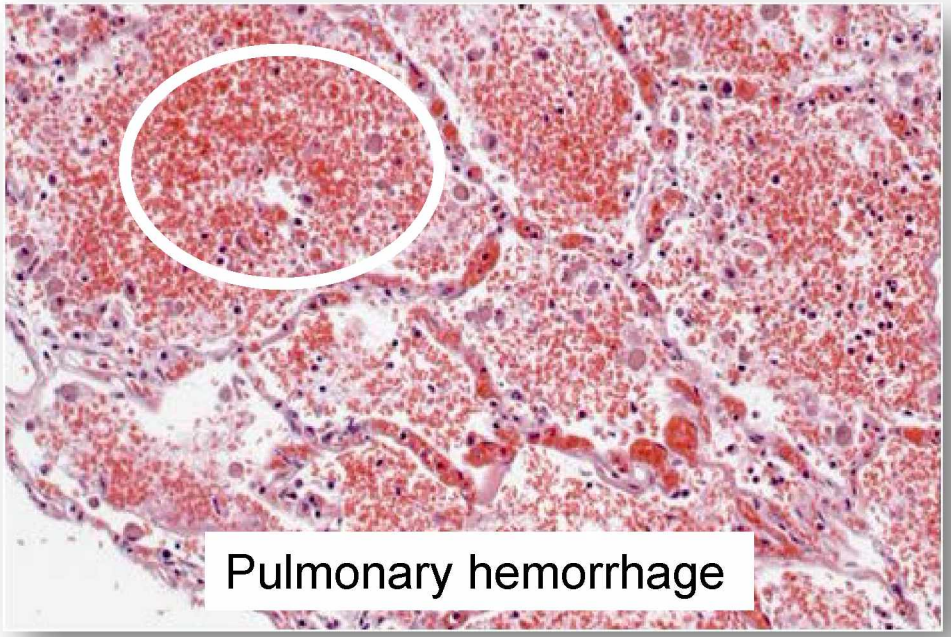
TRACKING A KILLER

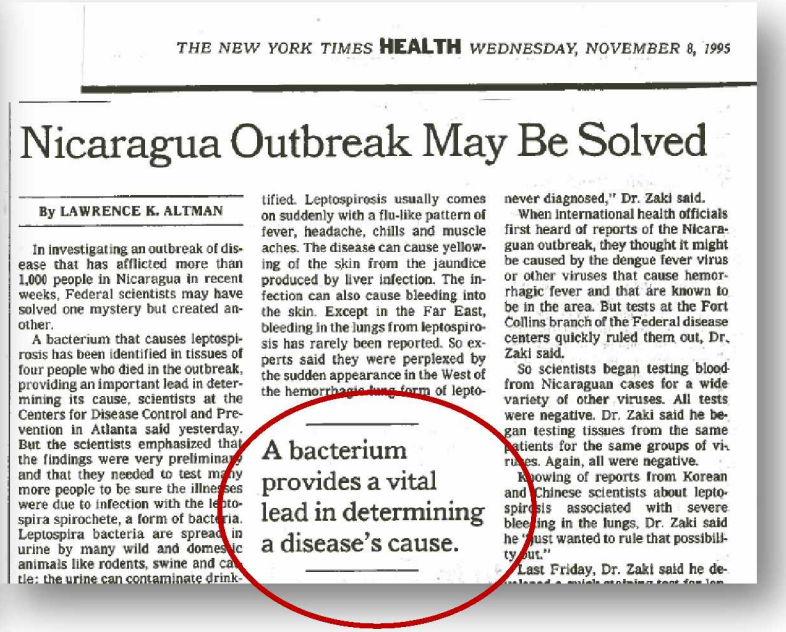
Health officials are trying to contain a mysterious virus that has swept through several towns in northern Nicaragua.

The Washington Times,
Tuesday, October 31, 1995

What We Did in 1995

- **Pathologic evaluation and testing at CDC aided in solving mystery outbreak of pulmonary hemorrhage**





THE NEW YORK TIMES **HEALTH** WEDNESDAY, NOVEMBER 8, 1995

Nicaragua Outbreak May Be Solved

By LAWRENCE K. ALTMAN

In investigating an outbreak of disease that has afflicted more than 1,000 people in Nicaragua in recent weeks, Federal scientists may have solved one mystery but created another.

A bacterium that causes leptospirosis has been identified in tissues of four people who died in the outbreak, providing an important lead in determining its cause, scientists at the Centers for Disease Control and Prevention in Atlanta said yesterday. But the scientists emphasized that the findings were very preliminary and that they needed to test many more people to be sure the illnesses were due to infection with the leptospira spirochete, a form of bacteria. Leptospira bacteria are spread in urine by many wild and domestic animals like rodents, swine and cattle; the urine can contaminate drinking

tified. Leptospirosis usually comes on suddenly with a flu-like pattern of fever, headache, chills and muscle aches. The disease can cause yellowing of the skin from the jaundice produced by liver infection. The infection can also cause bleeding into the skin. Except in the Far East, bleeding in the lungs from leptospirosis has rarely been reported. So experts said they were perplexed by the sudden appearance in the West of the hemorrhagic lung form of lepto-

A bacterium provides a vital lead in determining a disease's cause.

never diagnosed," Dr. Zaki said.

When international health officials first heard of reports of the Nicaraguan outbreak, they thought it might be caused by the dengue fever virus or other viruses that cause hemorrhagic fever and that are known to be in the area. But tests at the Fort Collins branch of the Federal disease centers quickly ruled them out, Dr. Zaki said.

So scientists began testing blood from Nicaraguan cases for a wide variety of other viruses. All tests were negative. Dr. Zaki said he began testing tissues from the same patients for the same groups of viruses. Again, all were negative.

Knowing of reports from Korean and Chinese scientists about leptospirosis associated with severe bleeding in the lungs, Dr. Zaki said he just wanted to rule that possibility out."

Last Friday, Dr. Zaki said he de-

The New York Times,
Wednesday, November 8, 1995

What We Did in 1995
Identified the Agent and Explained the Cause of Pulmonary Hemorrhage

- Novel IHC test used 16 reference rabbit polyclonal antisera reactive with majority of known leptospiral serovars
- Bacteria not easily cultured and takes about 6 weeks

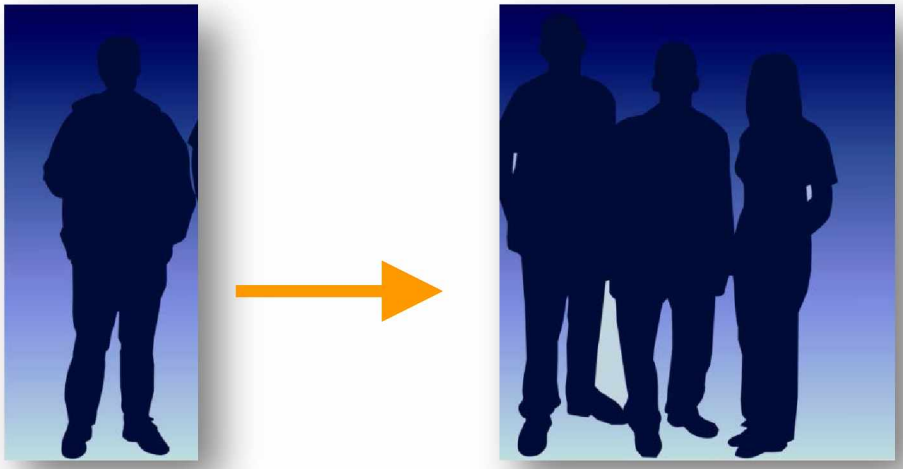
Leptospires (red) as visualized in lung with the newly developed IHC test

Zaki and W-J Shieh and Epidemic working group. Lancet 1996; 347:535-536

Today: Advanced Understanding of Leptospirosis

- **Pulmonary hemorrhage and leptospirosis is now a well recognized syndrome in addition to the "classic" hepatic and renal disease**
  - Recognition aids in treatment and saves lives
  - Recognition of increased transmission after intense rainfall and hurricanes helps disease control, prevention and community outreach
- **Common presentation in Central and South America, and Caribbean including Puerto Rico**
- **Several cases recognized during H1N1 pandemic 2009 in continental US**

Unexpected Donor-derived Infections Associated with Organ Transplantation



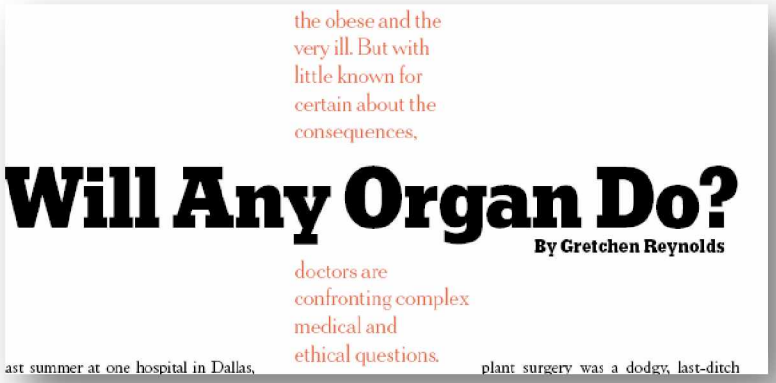
Single donor

Multiple recipients

- **Multiple challenges**
  - Unexpected/ unrecognized at time of death
  - Not screened for in donor
  - Unknown incidence (low)
  - High-profile events with significant morbidity and mortality

Unexpected Donor-derived Infections

NY Times, 2005 (rabies)



the obese and the very ill. But with little known for certain about the consequences,

Will Any Organ Do?

By Gretchen Reynolds

doctors are confronting complex medical and ethical questions.

ast summer at one hospital in Dallas, plant surgery was a dodgy, last-ditch

The New

Transplant Patients Die of Rodent Disease

The Virus, Undetected in Organ Donors, Is Linked to 6 Cases

By KATIE ZEZIMA and DENISE GRADY

Three organ recipients in southern ew England have died in the past

lance system for organ-transplant-transmitted infections." He added, "Without a clinician reporting it, we're not going to know."

transmitted West Nile virus.

At the Petsmart store in Warwick, 102 small rodents were removed this past weekend, and in preliminary

NY Times, 2005 (LCMV)

Officials Re-examining Organ Transplant Rules

Brain Infection in Two Patients Raises Issue

By DENISE GRADY

The plight of two kidney transplant patients who contracted a brain infection from an organ donor is prompting health officials to re-examine their policies on using people with certain neuro-

vising in the patients' treatment.

Dr. Matthew J. Kuehnert, the director of the office of blood, organ and other tissue safety at the disease centers, said that transplant patients are sometimes an early warning system for new in-

NY Times, 2009 (amoeba)

WEST NILE CASES RAISING QUESTIONS OVER TRANSPLANTS

NO TEST TO SCREEN BLOOD

Weeks Needed to Determine if Operation or a Transfusion Allowed Transmissions

NY Times, 2002 (WNV)

What We Did

Investigated and Identified Novel and Emerging Organ Transplant Transmitted Infections, 2002–2012

- **West Nile Virus: GA 2002**
- **Lymphocytic choriomeningitis virus**
  - WI 2003
  - MA and RI 2005
  - MA 2008
  - TX and OK 2011
- **Rabies: AL, AK, OK, TX 2004**
- **Balamuthia: MS and AZ 2009 and 2010**
- **Microsporidiosis: TX 2012**

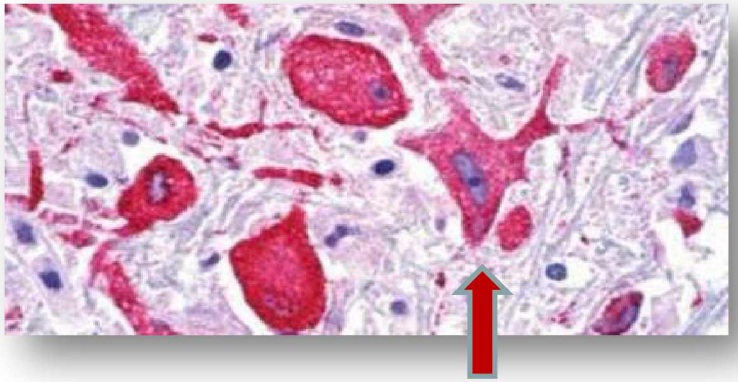
West Nile Virus Infection in an Organ Donor and Four Transplant Recipients, August 2002

Organ DONOR
- ✓ Female victim of a car accident
- ✓ Received multiple transfusions

→ **All organ RECEPIENTS (2 kidney, liver, heart) became febrile**

BUT, IHC showed WNV encephalitis

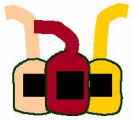
One kidney recipient
- ✓ Died of encephalitis
- ✓ Thought to have had WNV
- ✓ Seronegative for WNV



WNV antigen in neurons

Stimulated trace back investigations

Blood components from 63 donors



Only one component WNV IgM positive
Only one component WNV PCR positive, WNV IgM negative

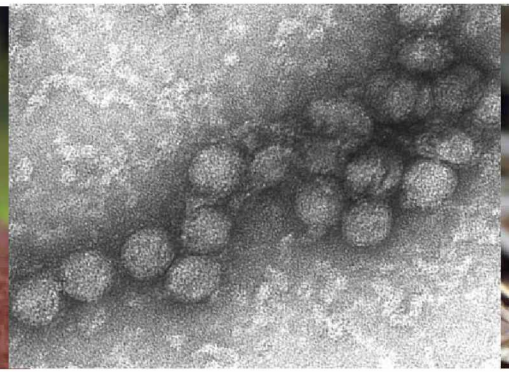
Iwamoto, M et al. NEJM 2003;348(22):2196-2203

Conclusions

- **Era of increased awareness of emerging and reemerging diseases**
- **Fundamental principles in recognition of these diseases**
  - Multidisciplinary approach
  - Traditional and state-of-the-art laboratory methods
- **Frontline role of pathology**
  - Recognition of emerging infectious diseases
  - Guiding epidemiologic investigations
  - Autopsies as a surveillance tool

Med-X: Medical Examiner Surveillance for Infectious Disease Mortality



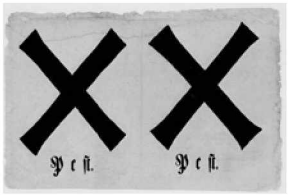



Kurt B Nolte, MD

Professor of Pathology, Assistant Chief for Research

Office of the Medical Investigator

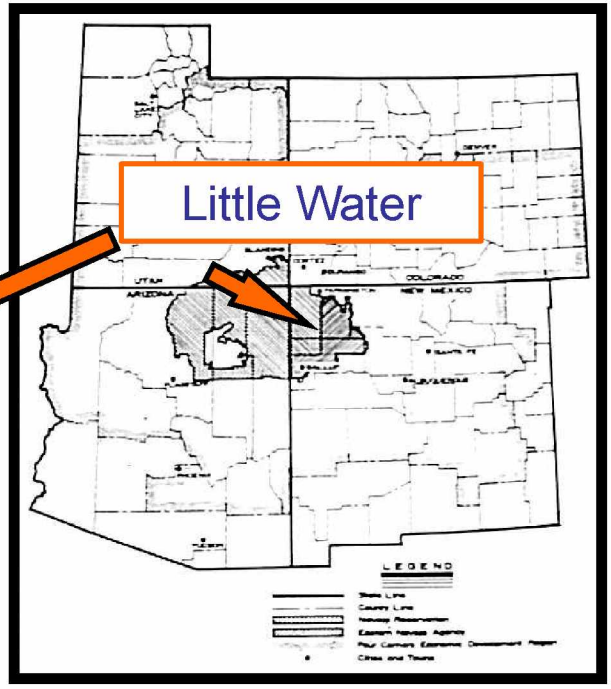
University of New Mexico School of Medicine



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

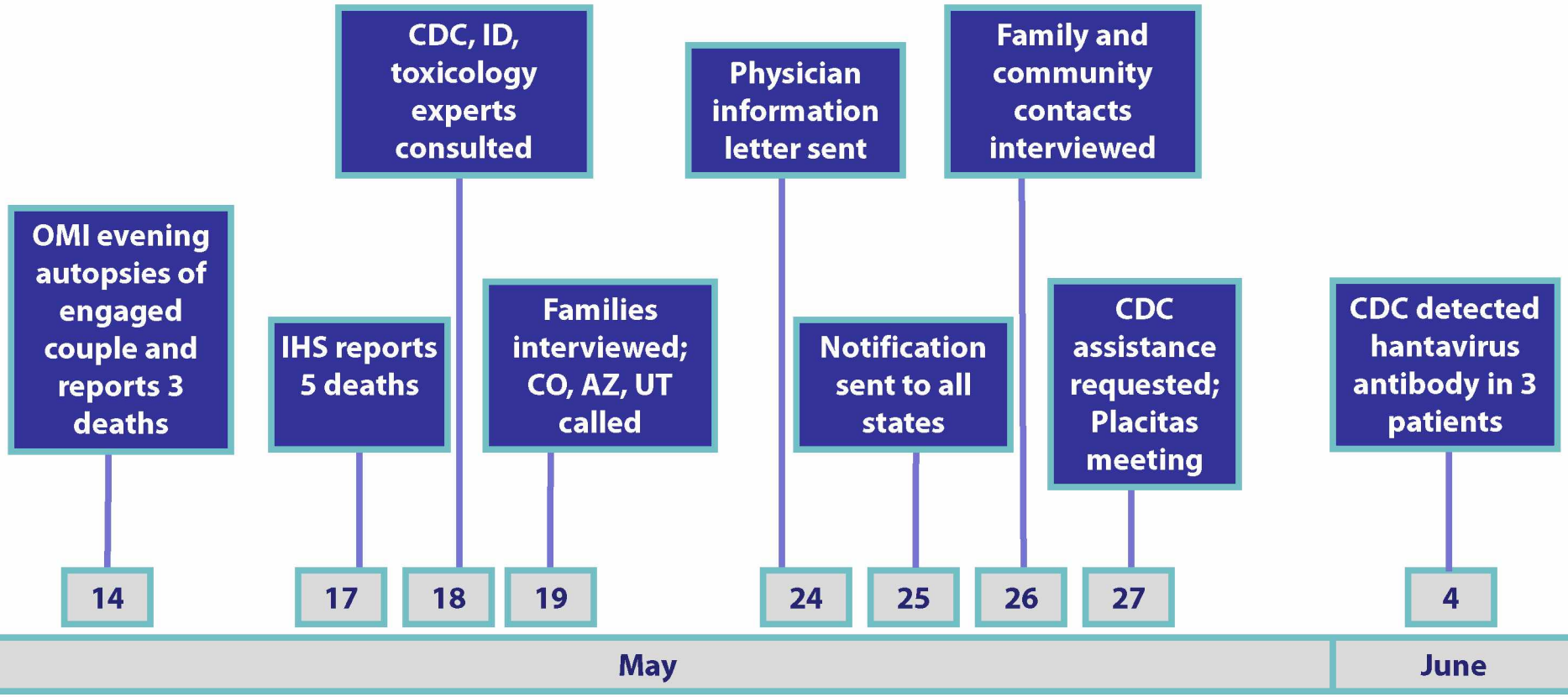
May 14, 1993

- 19 year old man died en route to fiancé's funeral
- Flu-like symptoms and abrupt shortness of breath
- Immediate night time autopsies
- Findings similar to case seen 1 month earlier



Nolte, KB et al. Arch Pathol Lab Med 1998;20:125-128

NM Unexplained Deaths, 1993



Medicolegal Death Investigative System

- Critical element: Recognizing fatal emerging infections and infections of public health importance
- Half of autopsies performed on persons who died of natural causes
- Infectious cause of death in 25% of natural disease autopsies*

*Nolte, KB et al. Arch Pathol Lab Med 1996;1120:125-128

Autopsy-based Surveillance Advantages Over Death Certificates

- **Use of human tissues allows for enhanced diagnostic capacity**
  - Accurate determination of cause of death
  - Insights into pathogenesis (e.g., HPS)
  - Insights into route of infection (inhalational anthrax)
  - Rapid public health notification of findings
  - More infections recognized than encoded by death certificates (e.g., TB)

HPS, Hantavirus pulmonary syndrome
TB, Tuberculosis

Med-X Surveillance

- **Evaluated 2000-2002**
- **Supported by CDC Bioterrorism Preparedness and Response Program**
- **Basic principles**
  - Uses surveillance symptoms to capture potential cases
  - Uses pathology-based syndromic reporting standards
  - Seeks organism specific diagnoses
  - CDC Infectious Diseases Pathology Branch provides enhanced diagnostic capacity

Nolte, KB et al. Hum Pathol 2007;38:718-725

Med-X Surveillance Symptoms

- Flu-like symptoms
- Fever and respiratory symptoms
- Acute encephalopathy or new onset seizures
- Descending paralysis, polyneuropathy
- New fatal rash
- New jaundice
- Acute bloody diarrhea
- Unexpected death

Nolte, KB et al. Hum Pathol 2007;38:718-725

Med-X Pathology-based Syndromes

Autopsy Syndrome	Potential BT Illness	Public Health Benefit
Community-acquired pneumonia	Plague Tularemia Q fever	Influenza Pneumococcal and other bacterial and viral pneumonias HPS
Acute respiratory distress syndrome	Inhaled *S. aureus* enterotoxin B Ricin Phosgene Chlorine Other gases	

Nolte, KB et al. Hum Pathol 2007;38:718-725
BT, Bioterrorism
HPS, Hantavirus pulmonary syndrome

Med-X Surveillance Results 2000–2002

6,104 jurisdictional cases

250 met entry criteria (4.1%)

141 had pathologic syndrome (56%)

127 had infectious disease (51%)

- Organism-specific diagnosis was made in 103 (81%) cases
- 60 (58%) were notifiable conditions in NM
  - 37 *S. pneumoniae*
  - 8 *S. pyogenes*
  - 5 *H. influenzae*
  - 1 *M. tuberculosis*
  - 1 botulism
  - *2* AIDS

Nolte, KB et al. Hum Pathol 2007;38:718-725

Positive Predictive Value of Med-X Symptoms

Surveillance Symptom	Number	Infectious Disease		Toxin		Other		Undetermined	
Flu-like symptoms	95	62	65%	6	6%	26	27%	1	1%
Fever and respiratory symptoms	60	43	72%	4	7%	11	18%	2	3%
Unexpected death	79	15	19%	12	15%	35	44%	17	22%
Encephalopathy or seizures	26	13	50%	6	23%	6	23%	1	4%

Nolte, KB et al. Hum Pathol 2007;38:718-725

Med-X Surveillance: Conclusions

- Flu-like symptoms, fever and respiratory symptoms, and encephalopathy or new-onset seizures

  are highly predictive of infections
- Sudden unexpected death is less likely to represent an infection
- Organism-specific diagnoses can be obtained in the majority of infectious disease deaths

Nolte, KB et al. Hum Pathol 2007;38:718-725

Med-X Surveillance: Conclusions

- **Uniform autopsy and reporting criteria increase recognition of public health conditions and likelihood of recognizing bioterrorism-related deaths**
- **Combined surveillance systems serve the public well, and can be tested, modified, and utilized daily**
- **Current Med-X Coverage in MN**
  - Used in 13% of large ME/C offices
  - Population served by system ~15 million

Nolte, KB et al. Hum Pathol 2007;38:718-725
Blau, DM et al. Intl Conf on EID, Atlanta 2010

Requirements to Implement Med-X

- Uniform area of medicolegal jurisdiction
- Linkage to a health department that shares the jurisdiction
- Uniform investigation of jurisdictional deaths
- Access to microbiology laboratory
- Electronic data management system

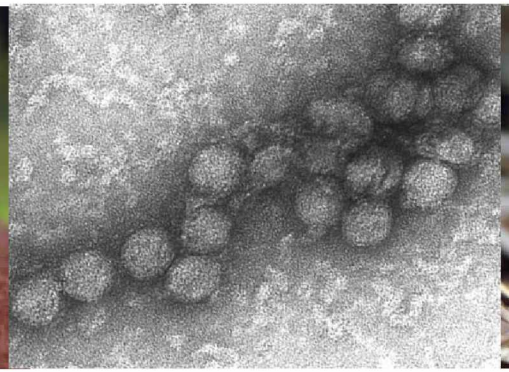
ME/C, Medical Examiner and Coroner
Nolte, KB et al. Hum Pathol 2007;38:718-725
Nolte, KB et al. Am J Forensic Med Pathol 2010;31:308-312

Let conversation cease,
let laughter flee,
for this is the place where
death delights to help the living.

Translation of Latin mosaic, Office of Chief Medical Examiner, City of New York

Unexplained Death Surveillance in Minnesota



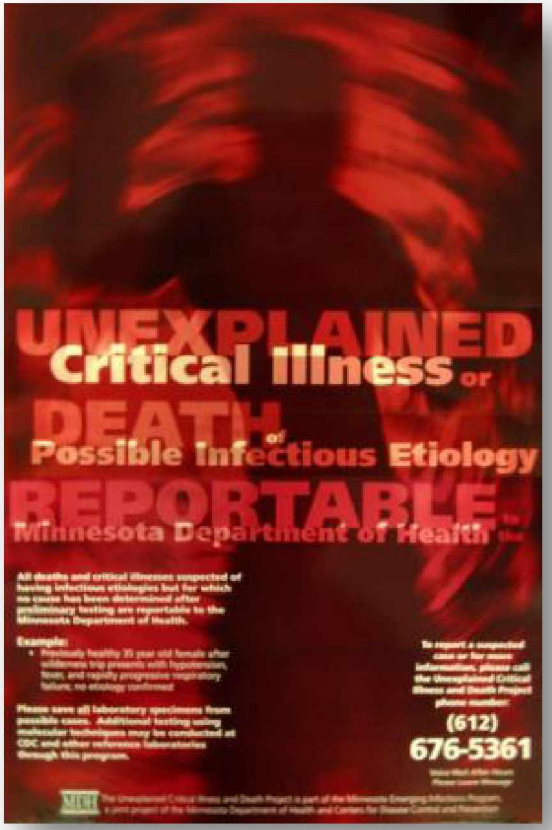



Ruth Lynfield, MD
State Epidemiologist and Medical Director
Minnesota Department of Health

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Overview

- Unexplained Death Surveillance in Minnesota
- Findings
- Lessons learned



http://www.health.state.mn.us/divs/idepc/dtopics/unexplained/index.html

Unexplained Death Surveillance (UNEX) in Minnesota

- **In 1995, UNEX started as part of the CDC Emerging Infections Program in 4 states: MN, CT, CA, and OR**
- **UNEX goals**
  - Identify novel and newly emerging pathogens
  - Identify deaths due to known pathogens presenting as sudden unexplained deaths
  - Monitor epidemiologic features of fatal infections
  - Improve pathology-based diagnostics

http://www.health.state.mn.us/divs/idepc/dtopics/unexplained/index.html

UNEX Case Definition

- **Death or critical illness unexplained by routine testing**
- **Pre- and/or post-mortem findings suggestive of an infectious disease**
  - Fever, leukocytosis, cerebrospinal fluid pleocytosis, or histopathological evidence of an infection
- **Focus on persons previously healthy and those <50 years of age, but not limited to that population**

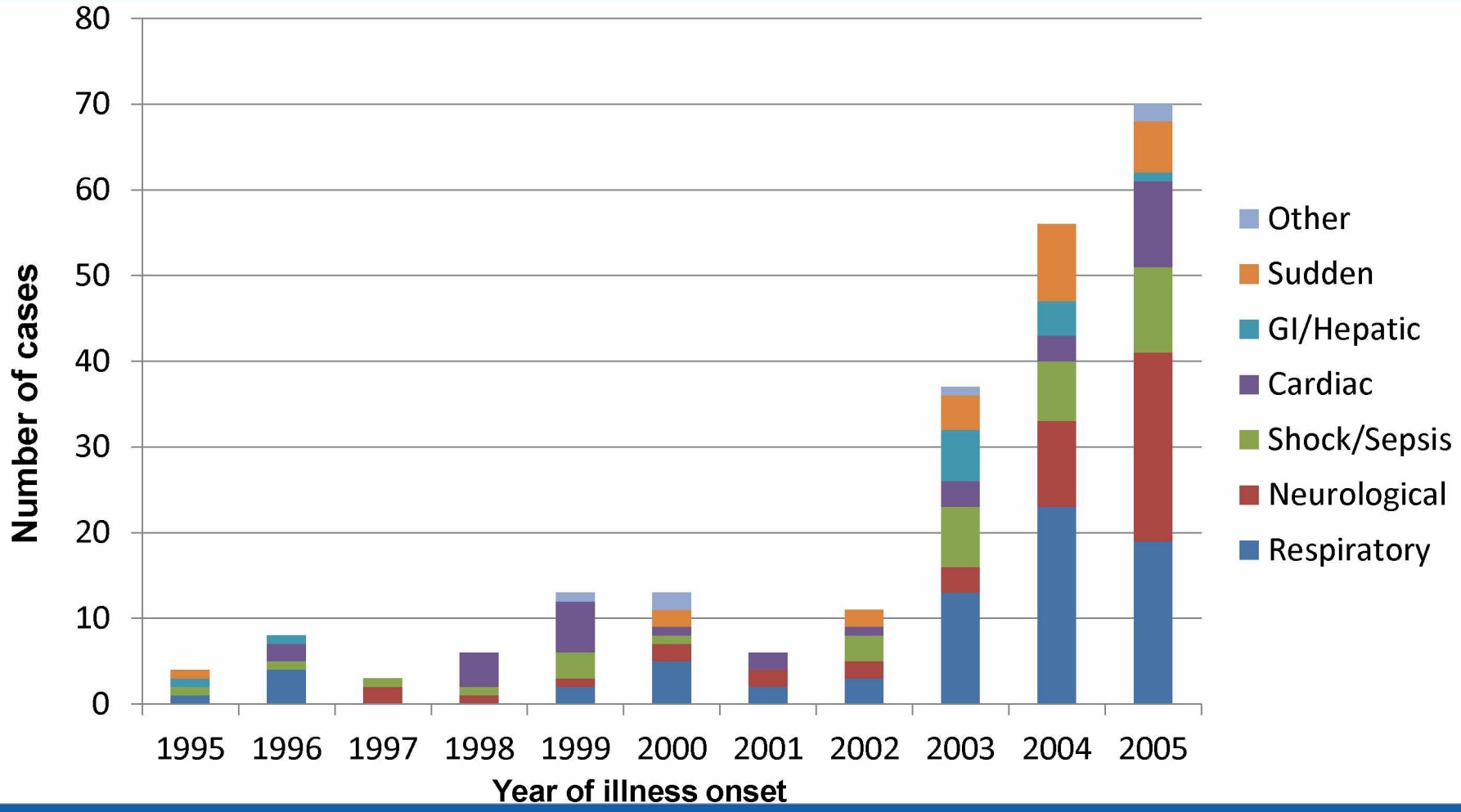
UNEX: Unexplained Death Surveillance

UNEX Case Finding and Investigation

- **Cases are reported to the MN Department of Health (MDH) by**
  - Infectious disease physicians
  - Infection preventionists
  - Hospital pathologists
  - Medical examiners
- **Information is collected from**
  - Medical records; Scene investigation findings
  - Autopsy and pathology reports
- **Specimens are tested at MDH laboratory and the CDC Infectious Diseases Pathology Branch (IDPB)**

UNEX: Unexplained Death Surveillance

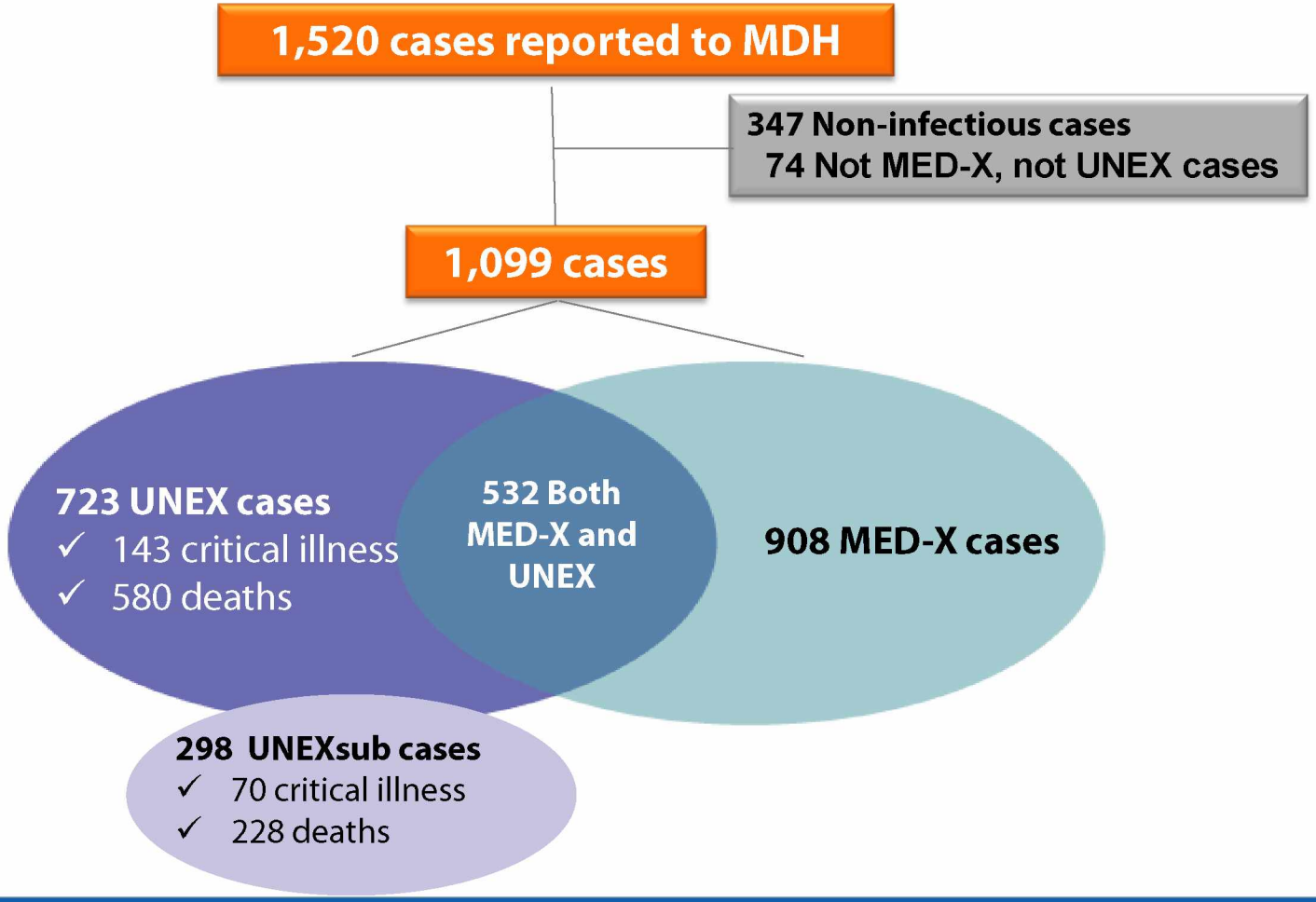
Unexplained Death and Critical Illness Surveillance in Minnesota, 1995–2005



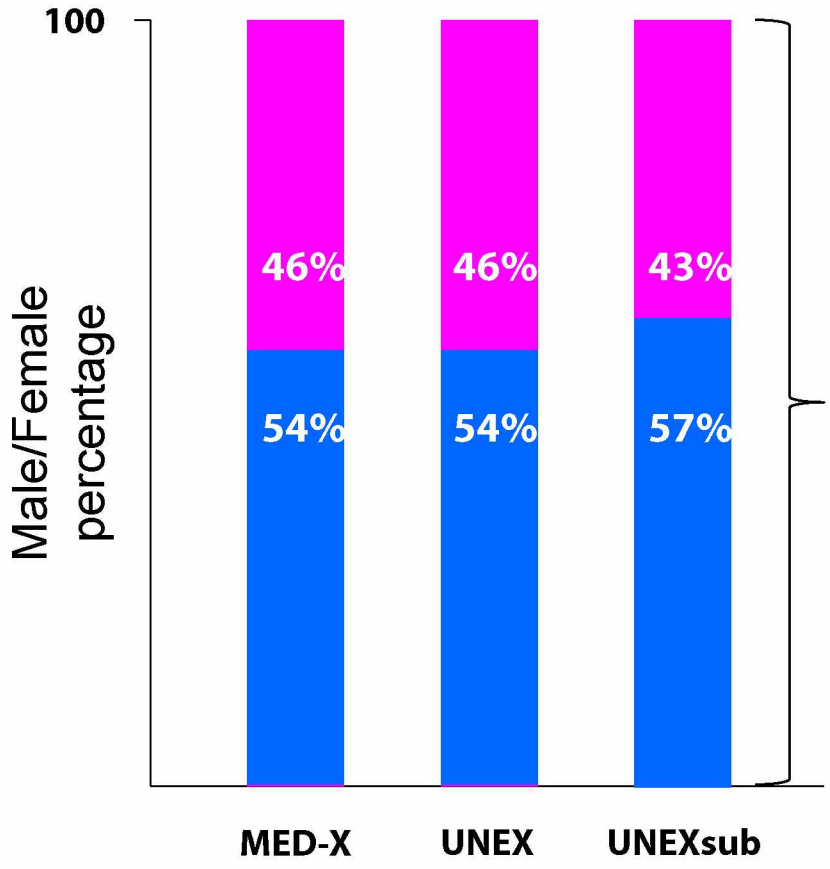
MED-X Case Finding and Investigation

- **In 2006, surveillance was initiated for all fatal infectious diseases in selected Medical Examiner (ME) jurisdictions (MED-X)**
  - Active surveillance conducted in partnership with the Minnesota Regional ME: Covers 8 counties, 14% MN population
    - During 2007-2010, rate of 12 infectious deaths/100,000 population
  - Minnesota Regional ME, Hennepin County ME, Ramsey County ME, Olmsted County ME and Midwest ME
- **MDH provides specimen collection materials with specimens sent to MDH**
- **NM MED-X model is used**

Unexplained Death and Critical Illness Surveillance in Minnesota, 2006–2011

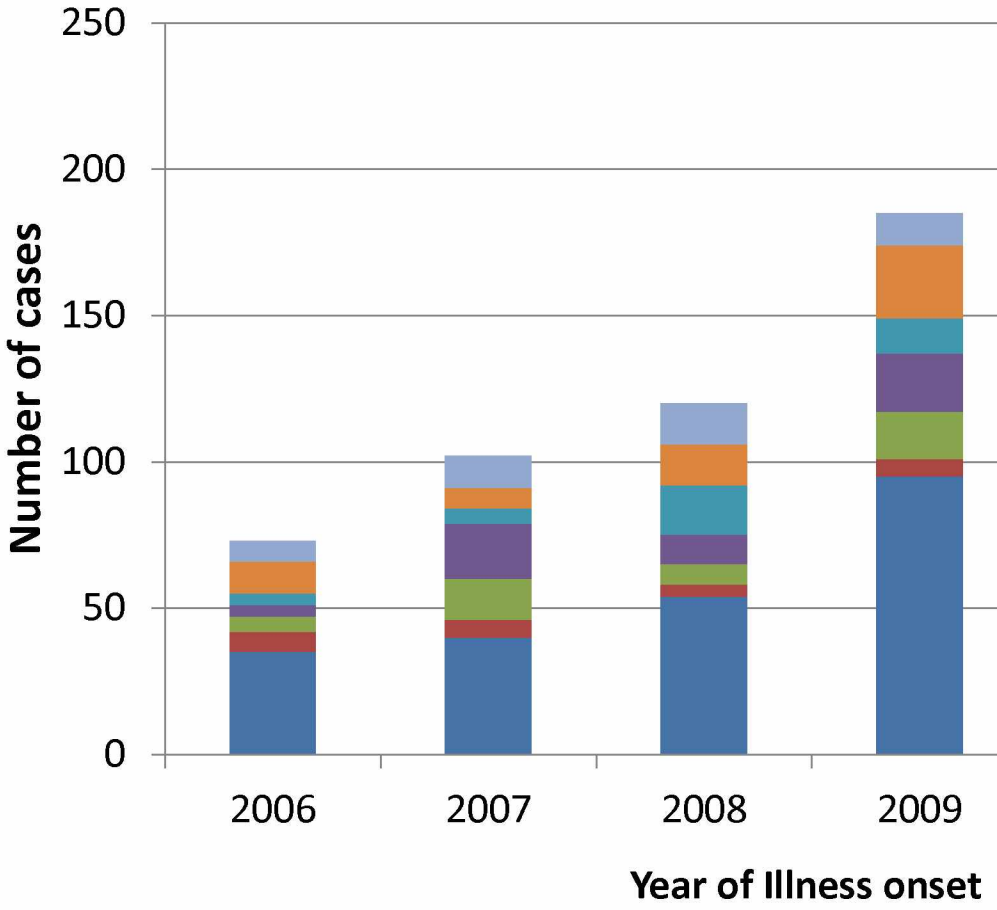


MED-X and UNEX, 2006–2011



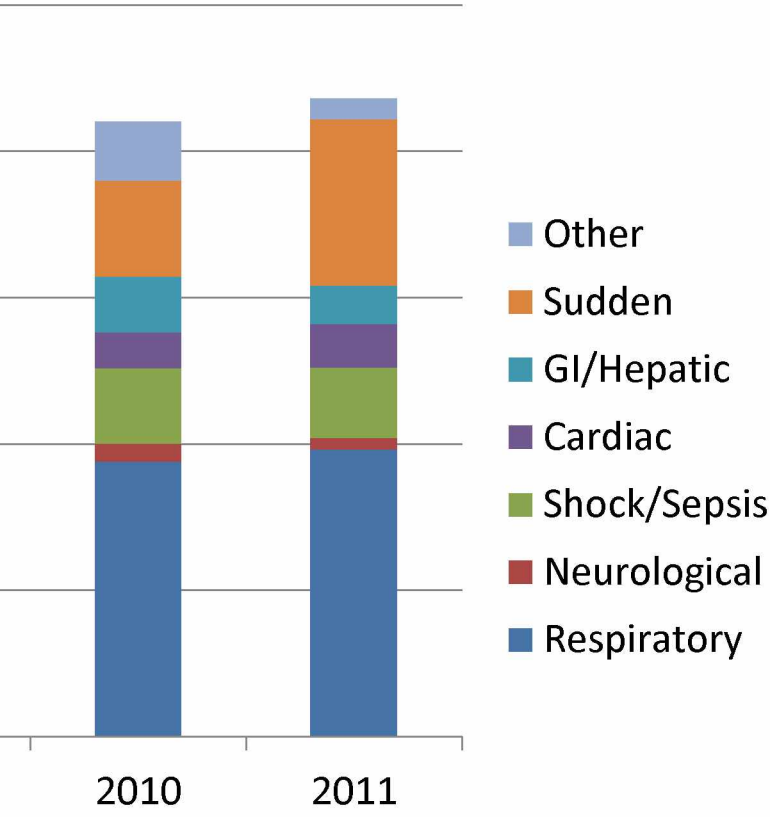
- **Median age 13 years (range 3 days–49 years)**
  - 228 fatal cases
    - 58% male
    - Median age 9 years
    - Range 3 days–49 years
  - 70 critical illness cases
    - 54% male
    - Median age 17 years
    - Range 12 days–47 years

Med-X Cases, 20

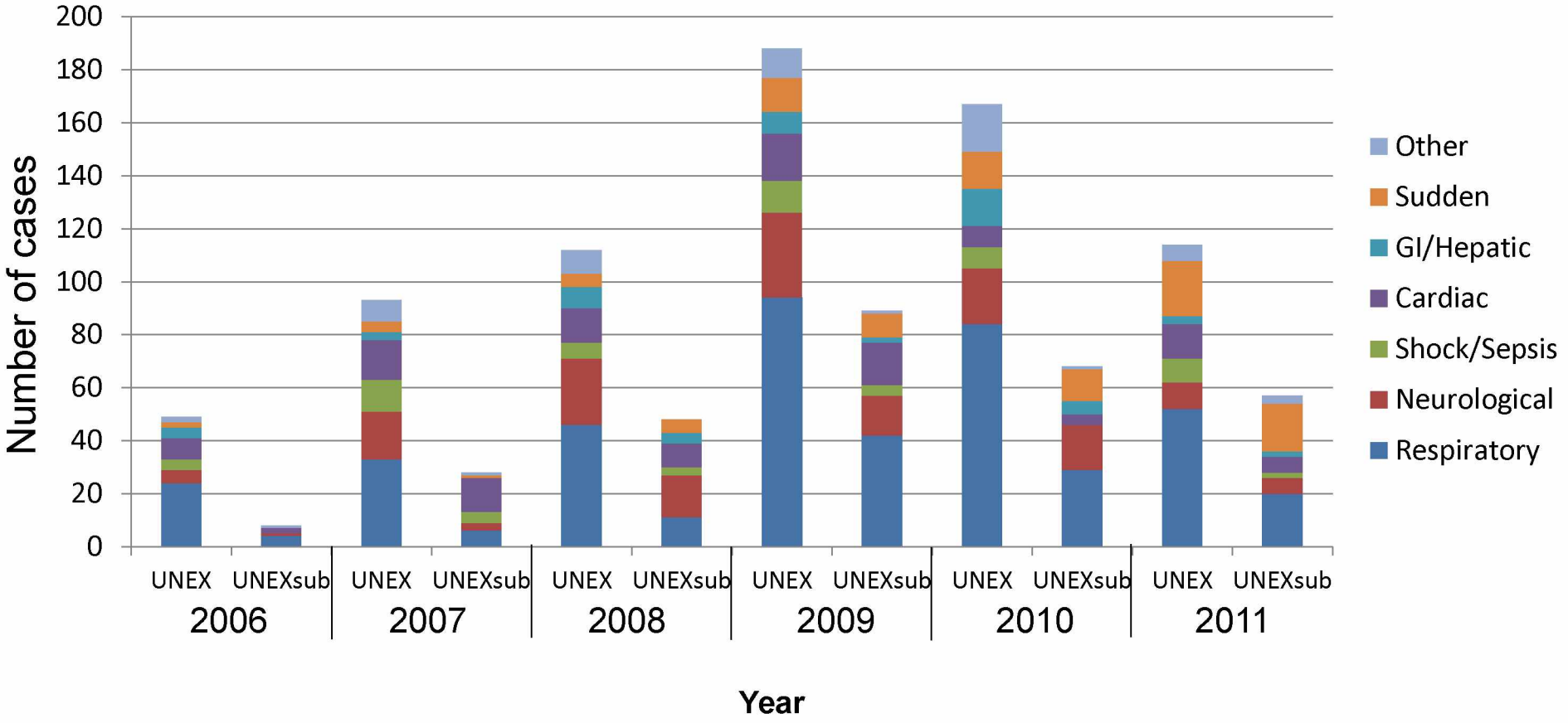


MED-X: Medical Examiner Jurisdictions

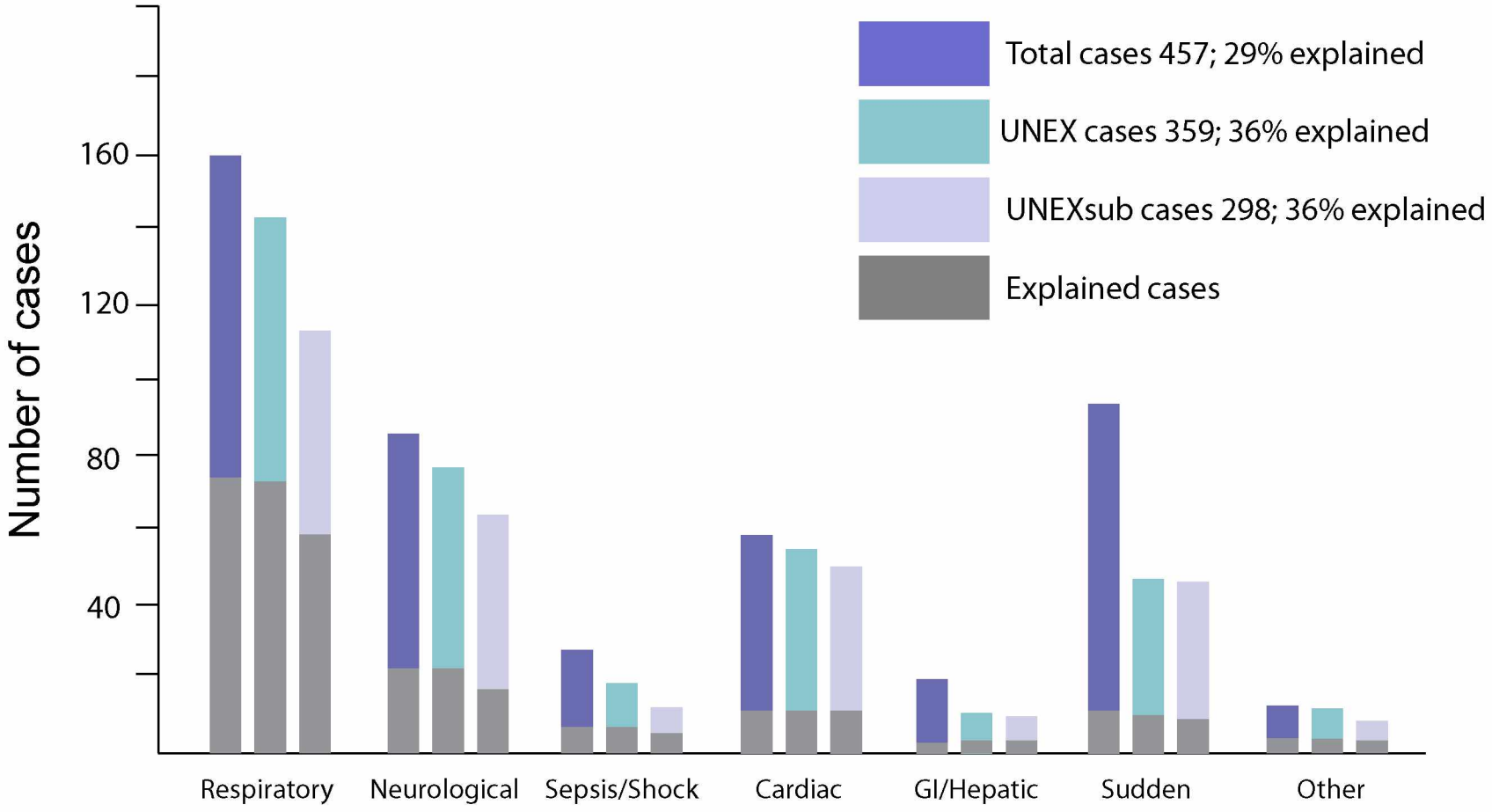
06–2011


Other
Sudden
GI/Hepatic
Cardiac
Shock/Sepsis
Neurological
Respiratory
2010
2011

UNEX and UNEXsub, 2006–2011

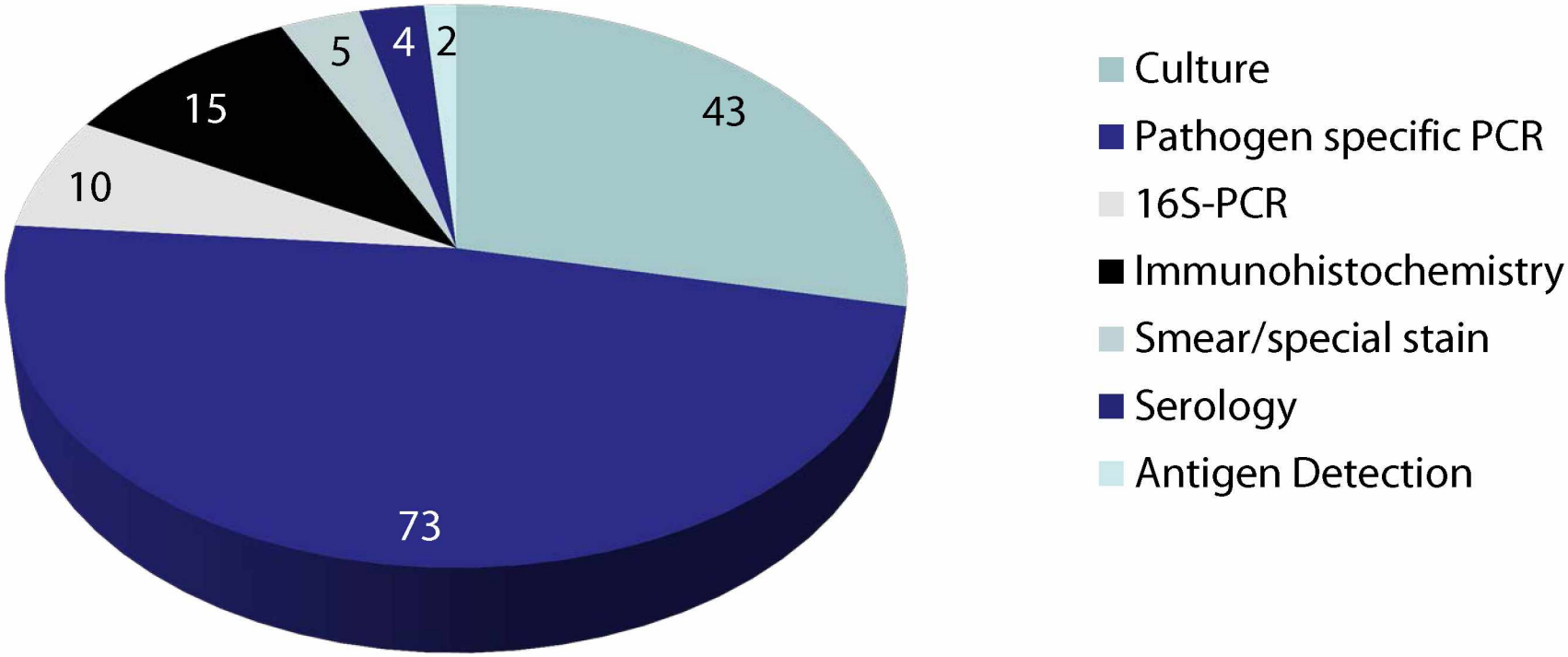


Frequency of Pathogen-Specific Explanation using Available Pre- or Post Mortem Specimens by Syndrome: 2006–2011*



*Includes definite and probable explained

Diagnostic Methods Used Among Explained UNEXsub Cases, 2006–2011 (n=106)



Sudden Unexpected Infant Death with Infectious Etiology: 2006–2011*

- **Includes Infant deaths with available specimens**
  - Often only fresh specimen was nasopharyngeal swab for respiratory viruses; however fixed tissue frequently available

Category	Explained	All cases	%
Respiratory	11	23	48%
Neurological	0	0	0%
Sepsis/Shock	1	2	50%
Cardiac	5	10	50%
GI/Hepatic	0	5	0%
Sudden	6	31	19%
Other	0	0	0%
Total	23	71	32%

*Includes definite and probable explained

Examples of Public Health Impact of Identifying Etiology among MN cases

- **Require specific public health interventions**
  - *Neisseria meningitidis*, polio (vaccine-derived poliovirus), *M. tuberculosis*
- **Vaccine preventable diseases**
  - *Streptococcus pneumoniae*, influenza
- **Nationally-notifiable infectious diseases**
  - Human Immunodeficiency Virus, *Legionella pneumophila*
- **New to Minnesota**
  - *Rickettsia rickettsii*, Powassan virus, *Naegleria fowleri*

Diseases New to Minnesota

- **Rocky Mountain Spotted Fever**
  - One of the cases had no travel history
  - Ticks collected and found to carry *Rickettsia rickettsii*
  - Educated physicians that Rocky mountain Spotted Fever may occur in MN
- **Powassan encephalitis**
  - Subsequent to detection of first case in 2008, developed diagnostic capacity and 14 other cases detected 2009–2011
- ***Naegleria fowleri***
  - 1st case in 2010; typically Southern States in United States
  - Educated physicians and the public about the disease
  - 2nd case occurred in 2012

Surveillance During 2009 H1N1 Pandemic

- **Specimens were evaluated from cases with influenza-like illness (ILI) based on pre-mortem symptoms and/or autopsy findings in MN UNEX/MED-X systems**
  - Testing conducted: Virologic testing, including PCR, culture
- **Laboratory surveillance for deaths among hospitalized patients with ILI was conducted**
- **Medical records and other data were reviewed to determine if H1N1 had been related to cause of death**
- **66 deaths were identified; 16 were found through UNEX/MED-X system**
  - Cases from UNEX/Med-X are younger, less likely to have underlying conditions, and more likely to be non-white

Lesson Learned

Partnering with medical examiners and pathologists to conduct infectious disease investigation and testing is especially important in identifying fatal infectious disease cases

Partnering with Medical Examiners and Pathologists

- **Case-based death investigation is unique in correlating laboratory findings, clinical features, and pathologic evidence to establish a causal relationship**
  - Cases of infectious disease of public health importance are detected that otherwise would likely be missed
  - Challenge: Sometimes identified pathogen(s) may not be cause of syndrome or death
- **Resource/labor intensive**
  - Medical examiners, pathologists, and public health staff
  - Additional testing and materials are required
- **Especially valuable when there is an emerging pathogen; e.g., influenza A (H1N1), Powassan virus**

Parting Thoughts

- **Emerging and reemerging diseases are well and alive!**
- **Critical components for their detection, prevention and control**
  - Vigilance and broad partnerships
  - Multidisciplinary approach
  - Advanced diagnostic tools

PUBLIC HEALTH GRAND ROUNDS

Office of the Director

September 18, 2012