Surveillance for Unexplained Deaths and Critical Illnesses Due to Possibly Infectious Causes, United States, 1995–1998


Population-based surveillance for unexplained death and critical illness possibly due to infectious causes (UNEX) was conducted in four U.S. Emerging Infections Program sites (population 7.7 million) from May 1, 1995, to December 31, 1998, to define the incidence, epidemiologic features, and etiology of this syndrome. A case was defined as death or critical illness in a hospitalized, previously healthy person, 1 to 49 years of age, with infection hallmarks but no cause identified after routine testing. A total of 137 cases were identified (incidence rate 0.5 per 100,000 per year). Patients’ median age was 20 years, 72 (53%) were female, 112 (82%) were white, and 41 (30%) died. The most common clinical presentations were neurologic (29%), respiratory (27%), and cardiac (21%). Infectious causes were identified for 34 cases (28% of the 122 cases with clinical specimens); 23 (68%) were diagnosed by reference serologic tests, and 11 (32%) by polymerase chain reaction-based methods. The UNEX network model would improve U.S. diagnostic capacities and preparedness for emerging infections.

The 1992 Institute of Medicine report—Emerging Infectious, Microbial Threats to Health in the United States (1)—highlighted the need for a more effective means to detect emerging infectious diseases. In response to this report and as part of the Emerging Infections Program (EIP) (2), the Centers for Disease Control and Prevention (CDC) collaborated with state health departments and academic institutions to develop a pilot surveillance strategy for early detection of new and unrecognized infectious diseases in the United States. This project—Surveillance for Unexplained Deaths and Critical Illnesses Due to Possibly Infectious Causes—was developed on the basis of two observations. The first was the realization that supposedly new infectious diseases identified in the United States in recent decades had been occurring long before they were recognized and identified. The second was important progress in molecular diagnostic methods, which in some instances has allowed new infectious agents to be identified and characterized with molecular probes, making in vitro cultivation unnecessary.

In 1995, we initiated population-based surveillance for unexplained deaths and critical illnesses due to possibly infectious etiologies (UNEX) at four U.S. sites. The objectives of this effort were to define the incidence, epidemiologic features, and possible causes of these deaths and illnesses; create a bank of clinical specimens for future testing as new pathogens and methods are identified; and assist in building U.S. capacity for detecting and responding to uncommon and previously unrecognized pathogens. This report describes the methods we developed to reach these goals and the results of the first 3.5 years of surveillance.

Methods

Surveillance Sites

Population-based surveillance for UNEX was initiated on May 1, 1995, among persons 1 to 49 years of age residing in the San Francisco Bay area (Alameda, Contra Costa, and San Francisco Counties) of California (n=2,168,810); in New Haven County, Connecticut (n=556,592); in the entire state of Minnesota (n=3,419,760); and among persons 1 to 39 years of age residing in Oregon (n=1,544,466).2 All these sites were participants in the EIP, and the total population targeted for

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2Oregon used a different age cut-off because of limited resources.
surveillance was 7.7 million. We report the results of surveil-

cance for cumulative cases through December 31, 1998.

Case Definition

An UNEX case was defined as illness in a previously

healthy resident of a surveillance area who was 1 to 49 years

old (1 to 39 years old in Oregon) and who died or was hospi-
talized with a life-threatening illness with hallmarks of an

infectious disease for which no cause was identified through

routine testing initiated by health-care providers. A previously

healthy person was defined as a patient without a preexisting

known systemic, chronic medical illness diagnosed before the

acute onset of the UNEX. Such preexisting conditions

included malignancy; HIV infection; chronic cardiac, pulmo-
nary, renal, hepatic, or rheumatologic disease; or diabetes mel-

litus. Patients were also excluded from the study if they had

received any immunosuppressive therapy, had evidence of
toxic ingestion or exposure, had trauma before their illness, or

acquired their illness ≥48 hours after hospital admission
(Appendix I).

A life-threatening illness was defined as any illness require-

ing admission to an intensive-care unit (ICU). Hallmarks of an

infectious disease were defined as the following: fever or his-
tory of fever, leukocytosis, histopathologic evidence of an

acute infectious process, or a physician-diagnosed syndrome

consistent with an infectious etiology, including encephalitis or

meningitis, fulminant hepatitis or hepatic failure, myocarditis,

adult respiratory distress syndrome, respiratory failure, or sepsis.

Case Finding and Ascertainment

Patients meeting the case definition were sought at surveil-

lance sites through various mechanisms. Practicing clinicians

in all surveillance sites were informed about the project

through letters and bulletins and presentations at local and

regional professional society meetings. Personnel at some sur-

veillance sites attempted to identify cases more actively

through regular communications with persons working in

ICUs and local medical examiners or through routine review

of ICU admission records. Physicians and other health profes-
sionals were asked to report suspected cases by telephone to

local surveillance site personnel. When a case was reported, a

screening form was completed to determine if the patient met

the case definition. This surveillance system was not designed
to provide timely reporting or testing.

Surveillance Audit

To evaluate the sensitivity of the surveillance system, per-

sonnel at all surveillance sites conducted a retrospective

review of death records from their surveillance areas, and three

sites (California, Connecticut, and Oregon) reviewed all hospi-
tal discharge data in their areas for a period of at least 1 year.

All death certificates for the age groups included in the sur-

veillance were reviewed for the presence of specific Interna-
tional Classification of Disease codes (ICD-9), selected for

their potential to identify unexplained deaths due to possibly

infectious causes (3). Persons whose death records included

ICD-9 codes indicating a disqualifying underlying medical

condition were excluded. Once potential cases were identified,

the patients’ medical records were reviewed. If the records

were not available, the primary physician was contacted to
determine if the patient met the surveillance case definition.

The sensitivity of the surveillance system for detecting deaths

(SD) was calculated by dividing the number of deaths (D1)
detected through surveillance alone by the total number of
deaths (D1+D2) detected through both surveillance and death

record review (D2): SD=D1/D1+D2. The sensitivity of the sur-

veillance system (SC) for detecting critical illness cases was
calculated by dividing the number of such cases (C1) detected

through surveillance alone by the total number of cases

(C1+C2) found through both surveillance and hospital dis-

charge review (C2): SC=C1/C1+C2.

Collection of Clinical Information and Specimens

For patients meeting the case definition, surveillance site

personnel completed a case report form that included demo-

graphic, epidemiologic, and clinical information. This infor-
mation was collected through interview of physicians caring

for the patient, review of the medical record, and contact with

the patient or the patient’s family. Cases were assigned a cli-

nical syndrome depending on the predominant system involved,
on the basis of information provided by the physician. These

syndromes included neurologic (encephalitis, meningitis), car-
diac (myocarditis, pericarditis, endocarditis), respiratory

(pneumonitis), and hepatic (hepatitis). Syndromes such as sep-
sis, in which no predominant organ system was involved, were
classified as “other.” The hospital laboratories were requested
to save all remaining clinical specimens obtained as part of
routine clinical management, including biopsies and autopsies.

Laboratory Testing

For the first 2 years of the study, the project investigators

selected diagnostic tests individually for each case. Decisions

were made on the basis of clinical, epidemiologic, and histo-

dologic data; previous laboratory testing ordered by the health-
care providers; and availability, timing, quality, and quantity of
clinical specimens. In the third year of the project, based on
information gained to date, a set of standardized syndrome-
specific laboratory testing protocols was developed for respi-

ratory, neurologic, cardiac, and hepatic syndromes (Appendix

II: available online at URL: http://www.cdc.gov/ncidod/EID/
vol8no2/pdf/01-0165-app2.pdf). These protocols prioritized
testing based on available clinical and epidemiologic informa-
tion and a differential diagnosis; they guided a first round of

laboratory testing which, if negative, prompted a customized
second round of testing. Cases that did not fit any of these four
syndromes were discussed by the project investigators on an
individual basis.
Histopathologic Testing
Whenever possible, in addition to initial examination by local pathologists, tissue specimens were examined by CDC pathologists to help guide further laboratory testing decisions. CDC pathologists have available a unique set of antibodies and probes for immunohistochemistry (IHC) and in-situ hybridization (ISH); these and other special studies, such as chemical stains, were selected based on all available case information. IHC tests were performed by a two-step indirect immunoperoxidase technique with various antibodies (4). ISH tests used digoxigenin-labeled probes with an immunoperoxidase staining protocol (5). Positive and negative controls were run in parallel with case specimens.

Testing for Viral Pathogens
The California Department of Health Services (CDHS) Viral and Rickettsial Diseases Laboratory was the primary testing site for viral pathogens other than the hepatitis viruses. Serologic tests were available for immunoglobulin (Ig) G directed against 19 viral pathogens and for IgM directed against 14 of these. When only a single serum specimen was available, the presence of both IgM and IgG was assessed, either by enzyme immunosorbent assay (EIA), indirect immunofluorescence assay (IFA), or both (6). Paired sera were tested by EIA or IFA for increase in IgG titer. Additional testing included nucleic acid amplification by polymerase chain reaction (PCR) for selected viral pathogens if adequate specimens were available (7-9). An increase in IgG titer by EIA was interpreted as evidence of recent or current infection if the ratio of convalescent- to acute-phase indices was $\geq 1.5$; an index is determined by the equation (optical density [OD] - positive antigen - OD-negative antigen)/predetermined positive threshold OD (usually 0.1). The CDHS diagnostic assays for IgM to B19V, Cytomegalovirus, Hantavirus (SNV), herpes simplex virus, MeV, MuV, RUBV, SLEV, VZV, and WEEV have varying minimum positive values, with indices from 1.0 and 2.0. For the enterovirus IgM assay, which detects the presence of enterovirus group antibody in serum, a ratio of OD-positive antigen to OD-negative antigen $\geq 2.6$ was considered positive. Agents tested by IFA were considered positive if a fourfold or greater rise in titer was detected. IFA IgM assays were considered positive if the staining pattern was distinct for that agent at the appropriate serum dilution.

Bacterial Broad-Range Ribosomal DNA (rDNA) PCR
DNA extraction from clinical specimens was performed as described (10,11). All clinical specimens tested with the broad-range bacterial rDNA PCR were analyzed by using at least one of the following primer pairs: fD1mod (positions 8-27 in Escherichia coli 16S rRNA gene) (12) and 16S1RR-B (575-556) (13); 8F2 (8-27) and 806R (806-787); and 515F (515-533) and 13R (1390-1371). PCR products were characterized by direct sequencing or cloning and sequencing, followed by comparison with rDNA sequences available in GenBank (11).

Criteria for Causation
Cases were defined as having definite, probable, possible, or no microbial etiology (Table 1). These levels of certainty for the causal role of an infectious agent reflected the integration of several factors, including the relationship of anatomic site of detection to site of disease, reliability of the method, and whether the putative agent was a known cause of the clinical syndrome under investigation. Cases were classified as explained if results showed a definite or probable disease cause and as unexplained if results indicated a possible infectious cause or none at all.

Statistical Analysis
Analysis was performed by SAS 6.12 (SAS Institute, Cary, NC). Denominators for the population under surveillance, obtained from the 1992 intercensus (14), included all persons in the age groups under surveillance at the various sites; denominators including only previously healthy persons are not available, and no attempt was made to estimate this frac-
were adjusted for age and race, this rate translates into 920 cases in the United States each year. The overall annual incidence rates remained stable over time, but varied among the different sites from 0.3 to 2.3 per 100,000 per year. The highest rate was in Connecticut, where active surveillance was conducted in a well-defined population of approximately 500,000 persons. Forty-one (30%) of the case-patients died, of whom 30 (73%) had autopsies performed, reflecting a rate much higher than the national autopsy rate of <11% (15). Cases were reported a median of 6 days from time of admission to the hospital (0 to 289 days).

The median age of case-patients was 20 years; 20 (15%) were 1 to 4 years of age, 53% were female, and 82% were white. The incidence rates varied by age group (Figure 1) but did not differ by sex and race. No differences were observed in the seasonal distribution of cases, nor was there clustering of cases by time or place. As for exposures, 54% of all cases were reported to have pets, which is similar to national rates of pet ownership: 54% to 64% (American Veterinary Medical Association U.S. Pet Ownership and Demographics Sourcebook); 8% had traveled outside the United States in the year before hospitalization, and 4% had received transfusions at least once in their lifetime.

**Clinical Features**

Table 2 summarizes the distribution of cases and the proportion explained by syndrome, as well as the syndrome-specific case-death ratios. The largest proportion of cases presented as a neurologic syndrome, followed closely by respiratory syndrome. The highest syndrome-specific case-death ratio was seen among cases with cardiac syndrome (46%) and the lowest among cases with neurologic syndrome (18%). An example of a case is described in Appendix III.

**Surveillance Audit**

Table 3 summarizes the results of the surveillance audits. The site-specific sensitivity (Sn) of our prospective surveillance for detecting unexplained deaths ranged from 38% in California to 100% in both Connecticut and Minnesota. Retrospective death record review identified 25% to 100% of all deaths detected through surveillance. Cases detected through surveillance but not by death record review were missed by the

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**Figure 1.** The incidence of cases by age group, 1995–1998, the Surveillance for Unexplained Deaths and Critical Illnesses Due to Possibly Infectious Causes Project (UNEX).
latter because the death certificates did not have the specified ICD-9 codes. The review of hospital discharge data focused on one tertiary-care referral hospital under surveillance in California and the one in Oregon, but included the entire surveillance area in Connecticut (16). Of potential cases identified by the selected ICD-9 codes, 90% to 96% were excluded, indicating the lack of specificity of these codes. The sensitivity of our prospective surveillance to detect only critical illnesses due to potentially infectious causes ($S_C$) was 13% to 73%. Retrospectively, the hospital discharge review was able to identify 41% to 81% of all cases detected prospectively through our surveillance.

### Search for Etiologic Agents

Of the 137 UNEX case-patients, 122 had specimens available for testing; 10 of these had tissue specimens only. Of the 122 cases, 34 (28%) could be attributed to a specific infectious agent; these agents were classified as definite or probable causes of the illness, based on our criteria (Table 1). Specific infectious causes and the laboratory methods used for diagnosis are listed in Table 4. Table 5 lists additional infectious causes for possible cases that did not meet our criteria for definite or probable causation. All the infectious agents identified in this study were previously recognized bacterial and viral pathogens. One patient, admitted because of syncope, was found to have a complete heart block and had evidence of simultaneous infection with *Borrelia burgdorferi* and *Ehrlichia chaffeensis*, which has been previously reported (17). A number of cases met the clinical definition for various infectious diseases syndromes, including toxic shock syndrome (five cases), but did not meet our definition for an explained case. In addition, four cases had evidence of polyclonal serologic response to multiple infectious agents and therefore could not be attributed to a specific etiology. The proportion of explained cases was largest among those with neurologic syndromes, followed by those with respiratory syndromes; it was higher among surviving patients (29%) than among patients who died (15%), although this difference was not statistically significant (p=0.2) (Figure 2). Explained cases were similar to unexplained cases in terms of patient age, sex, and race, but were reported sooner after admission than unexplained cases (median 4 vs. 7.5 days, respectively; p=0.1). The proportion of explained cases during 1998 (7 [17%] of 41), when laboratory testing protocols were used routinely for first-round testing, did not differ significantly from the same proportion for cases enrolled during 1995-1997 (27 [28%] of 96) when no such protocol was used (p>0.05).

Clinical specimens from each enrolled patient underwent an average of 28 laboratory tests (up to 103 tests). The mean number of tests performed did not differ substantially for explained and unexplained cases (30 vs. 27, respectively). None of the cases with only histologic specimens available had an infectious cause identified. Of the 34 explained cases, 23 (68%) were explained by using serologic tests, 7 (21%) by specific primer PCR, and 4 (12%) by 16S rDNA PCR. Among the 122 cases with specimens, serologic testing provided the highest yield in identifying infectious causes (23 [22%] of 104), followed by specific primer PCR (7 [10%] of 70) and 16S rDNA PCR (4 [8%] of 48). An infectious etiology was more likely to be identified in cases with paired serum specimens (14 [23%] of 62) than in those with single serum specimens (2 [5%] of 42) (p=0.05).

### Discussion

This study is the first to measure the population burden of unexplained deaths and critical illness from possibly infectious causes in the United States. To our knowledge, this is the first public health attempt to describe the features of this problem, in spite of its clinical complexities. This project established the infrastructure needed to detect UNEX cases, attempt to identify their etiology, and ultimately identify new infectious agents. However, since this project was a pilot study, it was difficult to standardize many of its aspects. Many lessons were learned during this project, whether related to the best surveillance methods to use or the laboratory testing process. In

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>No. (%)</th>
<th>No. of deaths (%)</th>
<th>Proportion of all deaths (%)</th>
<th>Sensitivity of prospective surveillance for unexplained deaths (%)</th>
<th>Sensitivity of prospective surveillance for critical illnesses (%)</th>
<th>Proportion of all unexplained deaths identified retrospectively through death record review (%)</th>
<th>Proportion of critical illnesses identified retrospectively by hospital discharge data review (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>39 (29)</td>
<td>7 (18)</td>
<td>15/37 (41)</td>
<td>38</td>
<td>25</td>
<td>63</td>
<td>75</td>
</tr>
<tr>
<td>Respiratory</td>
<td>36 (26)</td>
<td>11 (31)</td>
<td>13/33 (39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>28 (20)</td>
<td>13 (46)</td>
<td>3/22 (14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multisystem</td>
<td>18 (13)</td>
<td>4 (22)</td>
<td>3/15 (20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>9 (7)</td>
<td>4 (44)</td>
<td>0/8 (0)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (5)</td>
<td>2 (29)</td>
<td>0/7 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cases</td>
<td>137</td>
<td>41 (30)</td>
<td>34/122 (28)</td>
<td></td>
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</table>
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Table 4. Infectious disease causes for explained cases, UNEX, 1995–1998, California, Oregon, Connecticut, and Minnesota (n=34)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Etiology (n)</th>
<th>Tests (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>Neisseria meningitidis (4)</td>
<td>16S rDNA PCR (2), PCR (1), EIA IgM (1)</td>
</tr>
<tr>
<td>(n=15)</td>
<td>Bartonella henselae (1)</td>
<td>PCR, IFA IgG</td>
</tr>
<tr>
<td></td>
<td>Bartonella spp. (2)</td>
<td>IFA IgG</td>
</tr>
<tr>
<td></td>
<td>Chlamydia pneumoniae (1)</td>
<td>MIF IgG</td>
</tr>
<tr>
<td></td>
<td>Mycoplasma pneumoniae (1)</td>
<td>EIA IgM, IgM</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus (1)</td>
<td>EIA &amp; IFA IgG</td>
</tr>
<tr>
<td></td>
<td>Coxsackie B (1)</td>
<td>EIA IgM, viral culture</td>
</tr>
<tr>
<td></td>
<td>Enterovirus (1)</td>
<td>EIA IgM</td>
</tr>
<tr>
<td></td>
<td>Epstein-Barr virus b (1)</td>
<td>IFA IgG (VCA and EA)</td>
</tr>
<tr>
<td></td>
<td>Human herpes virus 6 (1)</td>
<td>IFA and EIA (IgM and IgG)</td>
</tr>
<tr>
<td></td>
<td>Mumps virus (1)</td>
<td>IFA IgM, IFA and EIA IgG</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Chlamydia pneumoniae (2)</td>
<td>MIF IgG (2), IFA IgM</td>
</tr>
<tr>
<td>(n=13)</td>
<td>Mycoplasma pneumoniae (4)</td>
<td>PCR (blood), EIA IgM/IgG</td>
</tr>
<tr>
<td></td>
<td>Streptococcus pneumoniae (2)</td>
<td>16S rDNA PCR (pleural fluid)</td>
</tr>
<tr>
<td></td>
<td>Legionella spp. (1)</td>
<td>PCR (from lung)</td>
</tr>
<tr>
<td></td>
<td>Adenovirus (1)</td>
<td>EIA and IFA IgG</td>
</tr>
<tr>
<td></td>
<td>Influenza B virus (1)</td>
<td>EIA and IFA IgG</td>
</tr>
<tr>
<td></td>
<td>Influenza A virus (1)</td>
<td>EIA and IFA IgM, IgA (IgG)</td>
</tr>
<tr>
<td></td>
<td>Human parainfluenza virus types 1 and 3 (1)</td>
<td>EIA and IFA IgG</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Borrelia burgdorferi/ Ehrlichia chaffeensis (1)</td>
<td>EIA/IFA flagella IgG, Western blot (IgG, IgM)</td>
</tr>
<tr>
<td>(n=3)</td>
<td>Enterovirus (1)</td>
<td>EIA IgM</td>
</tr>
<tr>
<td></td>
<td>Legionella spp. (1)</td>
<td>PCR (heart)</td>
</tr>
<tr>
<td>Multisystem</td>
<td>Neisseria meningitidis (1)</td>
<td>PCR (CSF)</td>
</tr>
<tr>
<td>(n=3)</td>
<td>Adenovirus (1)</td>
<td>PCR (blood)</td>
</tr>
<tr>
<td></td>
<td>Enterovirus (1)</td>
<td>IgM EIA</td>
</tr>
</tbody>
</table>

*EIA = enzyme immunosorbent assay, IFA = indirect immunofluorescent assay, IG = immunoglobulin, MIF = microimmunofluorescence, PCR = polymerase chain reaction.

*bSee Appendix III for a detailed description of this case.

addition, data obtained in the first 3.5 years of this project suggest that UNEX occur in previously healthy persons at rates similar to those of other conditions of clear public health concern and priority (18). Of obvious concern is also the large proportion of these deaths and severe illnesses that remains unexplained after extensive laboratory testing. Our findings highlight the substantial limitations of available diagnostic tests for infectious diseases and the need for improved tests and novel approaches to identify infectious disease agents.

Our surveillance estimated the burden of disease only among previously healthy persons 1 to 49 years of age. Since a different age cut-off was used in Oregon, the final rates of disease were adjusted for age and race. The lower age limit was chosen to avoid confusion with congenital problems seen in infants but to include most children in day care, where infectious diseases are common and new infectious diseases might spread rapidly. The upper age limit was intended to exclude an expected increased proportion of unexplained deaths due to noninfectious causes among persons ≥50 years of age. Although immunocompromised patients are more susceptible to a variety of infectious diseases, available resources and a concern that the clinical relevance of novel microbial findings would be more difficult to interpret in immunocompromised persons compelled us to focus on previously healthy persons. In addition, many of the new infectious diseases first identified in these persons have subsequently been found to affect persons with normal immune systems (19,20).

The surveillance methods adopted during this project were customized to meet the objectives of this study, taking into consideration the limitations of local resources; therefore UNEX cannot be easily compared with other classical surveillance systems. The different methods of surveillance used at the four sites allowed us, through the surveillance audits and validation, to determine how these differences affected case-finding. For example, investigators in Connecticut were able to detect most UNEX cases largely because they conducted more active surveillance in a smaller population base; in this site, surveillance focused on all seven hospitals in New Haven County. At the academic tertiary-care hospital, EIP staff reviewed ICU admission logs and communicated with clinicians daily. At the other six hospitals, a stimulated passive surveillance system was used in which physicians and infection control practitioners were given reminders several times per year. The active prospective method captured a greater proportion of total cases (86% of cases at the single hospital) than did the passive methods (50% of total cases at the six remaining hospitals).

If this surveillance is to be expanded, different methods may be chosen, depending on availability of resources and overall objectives. Less resource-intensive passive surveillance may be used if the goal is to monitor trends in disease occurrence. For example, although analyzing all death certifi-

Table 5. Infectious disease causes for “possibly” explained cases, UNEX, 1995–98, California, Oregon, Connecticut, and Minnesota (n=34)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Etiology (n)</th>
<th>Tests (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>Mycoplasma pneumoniae</td>
<td>Remel EIA (IgM/IgG)</td>
</tr>
<tr>
<td></td>
<td>Influenza B virus (FLUBV)</td>
<td>Nasopharyngeal culture</td>
</tr>
<tr>
<td></td>
<td>Varicella-zoster virus (reactivation)</td>
<td>EIA/IFA IgG</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Enterovirus</td>
<td>EIA IgM</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Chlamydia pneumoniae</td>
<td>MIF IgG</td>
</tr>
<tr>
<td></td>
<td>Adenovirus</td>
<td>EIA IgM</td>
</tr>
<tr>
<td></td>
<td>FLUBV</td>
<td>IFA IgM</td>
</tr>
<tr>
<td>Otherb</td>
<td>Enterovirus (2)</td>
<td>IgM EIA</td>
</tr>
</tbody>
</table>

*EIA = enzyme immunosorbent assay, IFA = indirect immunofluorescent assay, IG = immunoglobulin, MIF = microimmunofluorescence, PCR = polymerase chain reaction.

*bOther syndromes included one case with thrombotic thrombocytopenic purpura and one with hemolytic uremic syndrome.
investigation could substantially decrease the workload. Under
ner of death was recorded as natural, undetermined, or pending
electronically searching only the certificates in which the man-
that found in our study (0.5 per 100,000) is likely due to the
100,000 population. The discrepancy between this rate and
among healthy persons 1 to 49 years of age was 8.9 per
these EIP sites (3). In 1992, the rate of unexplained deaths
lance populations at the four sites. Second, the differences in
expected that the incidence of UNEX found in this study repre-
all rate detected was a minimal estimate of overall disease.
An important unresolved issue from our study is the large
proportion of cases that remained unexplained, even after
extensive laboratory testing. Although a standardized protocol
for testing was used only during 1998, the proportion of
explained cases before and after this protocol was used did not
differ substantially. Some illnesses may have noninfectious
causes, especially given the lack of specificity in our clinical
criteria for case inclusion and in the features of infection in
general. In cardiac syndromes, for example, myocarditis and
myocardial infarction can have very similar presentations.
Some cases may have been caused by microbial products such
as toxins without the presence of the organism or substantial
amounts of its nucleic acids. Laboratory methods for screening
and detection of toxins remain inadequate. For some patients,
specimens were not available from the primary site of disease,
were severely limited in quantity, or were only available from
late in the course of the disease; in many cases, multiple serum
specimens were not available, autopsies were incomplete, and
tissue specimens were obtained only from unaffected organs.
Finally, the breadth of our testing methods may not have been
adequate. Since broad-range PCR methods were applied only
to bacteria and a limited range of viruses, many other potential
agents may have been missed. Our approach to the detection
of viral pathogens relied more heavily on serologic and immu-
nohistochemical techniques, in part because of the difficulty in
designing a comprehensive set of consensus PCR primers for
all known viral families (21). In our study, viral testing was
also constrained by limited experience with certain IgM
assays. The development, testing, and application of compre-
prehensive broad-range viral and fungal consensus primers for
use in PCR assays may be helpful. Through this project, we
created a population-based bank of clinical specimens that
may prove valuable in the search for newly recognized etio-
logic agents, the development of diagnostic tests, and the stan-
ardization of nucleic acid-based techniques for identifying
previously unknown etiologic agents.

This project represents an attempt to build capacity for
early detection and response to emerging infectious diseases
threats in the United States and elsewhere. The usefulness of
this surveillance system for UNEX was recently illustrated
during an outbreak of West Nile virus encephalitis in the
northeastern United States (22) and an outbreak of unexplained
illness among injecting drug users in Scotland and Ireland (23);
initial reports of illness from both these investigations were
received through the UNEX surveillance project, and initial
testing was conducted through the infrastructure developed for
this project. Future surveillance for UNEX may benefit from
simplified case-finding methods, improved specimen quality,
and more focused syndrome-specific surveillance. Once vali-
dated, surveillance methods may be adopted by the broader
public health community. Such surveillance approaches will
strengthen the collaboration between clinicians, laboratorians,
and public health professionals, leading to improved detection
of unexplained deaths and critical illnesses, including possible
bioterrorism events, and better monitoring of emerging infec-
tious diseases.

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Appendix I

Case Definition, Surveillance for Unexplained Deaths and Critical Illnesses Due to Possibly Infectious Causes, United States, 1995–1998

Previously Healthy

Patients are considered previously healthy who had no known preexisting chronic medical condition before the onset of the illness resulting in hospitalization or death, including malignancy; HIV infection; chronic cardiac; pulmonary, renal, hepatic, or rheumatologic disease; or diabetes mellitus. These patients have no history of immunosuppressive therapy, trauma thought to be related to illness, evidence of toxic ingestion or exposure, or nosocomial infection.

Reasons for Exclusion

1. A history of a malignancy other than nonmelanoma skin cancer
2. HIV infection identified during hospitalization, previously or after discharge
3. History of physician-confirmed myocardial infarction, angina with known coronary artery disease, or congestive heart failure
4. Any history of hospital admission for asthma or other pulmonary diseases except for uncomplicated pneumonia
5. History of dialysis or chronically elevated blood urea nitrogen and creatinine
6. Biopsy-proven liver disease of any kind or chronic coagulopathy or chronic Hepatitis B or C virus infection as a result of hepatic insufficiency
7. Physician-confirmed rheumatologic conditions requiring chronic or intermittent medical therapy with oral steroids or other immunosuppressive drugs
8. Any known physician-confirmed diabetes mellitus previously or during hospitalization
9. Development of hallmarks of infection >48 hours after hospital admission
10. Any mention of a history of excessive alcohol use, alcohol abuse, or alcoholism is a reason for exclusion (e.g., delirium tremens, withdrawal seizures, alcoholic neuropathy, persistent liver function test abnormalities, gastrointestinal bleeding, coagulopathy, or hypoalbuminemia).
11. Any mention of injecting drug use
12. Any history of neurologic disease, including seizures,
13. Obesity, defined as body mass index ≥30 or "obese" noted in medical chart
14. Physician-confirmed diagnosis of anorexia

Not Reasons for Exclusion

1. Hypertension or a history of hypertension
2. Any history of inhaler use
3. Pyelonephritis or nephrolithiasis or a history of either of these conditions in the absence of a chronically elevated blood urea nitrogen and creatinine
4. History of hepatitis
5. Pregnancy

Appendix II

Algorithm for Meningo-Encephalitis available online only at URL: http://www.cdc.gov/ncidod/EID/vol8no2/pdf/01-0165-app2.pdf

Appendix III

An Example of a Clinical Case Surveillance for Unexplained Deaths and Critical Illnesses Due to Possibly Infectious Causes, United States, 1995–1998

A 22-month-old boy from Oregon was healthy except for previous bouts of otitis media, for which tympanostomy tubes had been placed. Three days before admission, in May 1997, tactile fever was noted, and one day before admission, the patient had decreased activity and rhinorrhea. On the day of admission, he vomited twice. In the emergency room, he had a temperature of 39.2°C, was irritable and lethargic, and had nuchal rigidity. A complete blood count showed a total leukocyte count (WBC) of 18,300 (69% segmented cells, 8% bands). Cerebrospinal fluid (CSF) analysis showed a WBC of 54 (25% segmented cells, 75% monocytes), protein 38 mg/dL, and glucose 70 mg/dL. The patient was hospitalized and initially treated with ceftriaxone. On the next day, he became less responsive, and abnormal posturing developed in the left upper and lower extremities. A computed tomography scan of the head (without and with contrast) was normal. He was transferred to a tertiary-care center, where an electroencephalogram showed moderate generalized slowing and recurrent right hemispheric electrographic seizures. A magnetic resonance imaging scan done on the same day showed a diffusely increased white matter signal consistent with viral encephalitis or acute disseminated encephalomyelitis. The patient received acyclovir for 3 days. His responsiveness and clinical condition gradually improved, and he was transferred to a rehabilitation service 17 days after admission. Initial work-up at the hospital revealed negative blood cultures and negative bacterial and viral cultures of the CSF. PCR for Epstein-Barr virus in the blood and CSF was negative, as was PCR for herpes simplex virus in CSF.

The patient was enrolled in the UNEX project and evaluated. Specimens available for testing included acute- and convalescent-phase serum and CSF specimens. A variety of tests were conducted (see neurologic syndrome testing protocol in Appendix II). Because the quantities of specimens available were limited, testing was prioritized. First-round testing was negative for Cytomegalovirus, HHV-6, and arboviruses. However, testing for IgG antibodies (by IFA) for Epstein-Barr viral capsid antibodies showed a fourfold rise in titer between acute- and convalescent-phase serum specimens; testing for IgG antibodies (also by IFA) to Epstein-Barr early antigen revealed a fourfold decrease in titer between convalescent- and acute-phase serum specimens, indicating acute Epstein-Barr infection.

Emerging Infectious Diseases • Vol. 8, No. 2, February 2002 153