Determinants for Autopsy after Unexplained Deaths Possibly Resulting from Infectious Causes, United States

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We analyzed US multiple cause-of-death data for 2003–2006 for demographic and clinical determinants for autopsy in unexplained deaths possibly resulting from infectious causes. For 96,242 deaths, the definition for unexplained death was met and autopsy status was recorded. Most decedents were male, 40–49 years of age, and white. To identify factors associated with unexplained death, we used data from Arizona records. Multivariate analysis of Arizona records suggested that decedents of races other than white and black and decedents who had clinicopathologic syndromes in the cardiovascular, sepsis/shock, and multisyndrome categories recorded on the death certificate were least likely to have undergone autopsy; children with unexplained death were the most likely to have undergone autopsy. Improved understanding of unexplained deaths can provide opportunities for further studies, strengthen collaboration between investigators of unexplained deaths, and improve knowledge and awareness of infectious diseases of public health concern.

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Many factors can influence the dynamics of pathogen ecology, increase the mobility of microbial agents, and elevate the risk for infectious disease posed to humans. Outbreaks and novel pathogens identified in recent decades are reminders that historical and newly recognized

infectious diseases remain threats to the health of the global community (*1–3*). Unexplained deaths possibly resulting from infectious causes (unexplained deaths) also present public health challenges. Many fatal infectious etiologies are never identified because of inadequate testing or inherent difficulties of detecting certain pathogens (*4*).

An autopsy can verify an existing diagnosis or provide a diagnosis if one is not determined before death, which might facilitate provision of prophylaxis or treatment of contacts of decedents with communicable diseases. Autopsies also contribute to epidemiologic data, provide insights into disease pathogenesis, and create educational opportunities for physicians and medical students (*5*). Recent disease descriptions facilitated by autopsy findings include hantavirus pulmonary syndrome, West Nile virus, and severe acute respiratory syndrome (SARS) (*6–8*); pathogens for these diseases were recognized only after substantial numbers of illnesses and deaths. Although autopsies of persons who died of unexplained causes can help build public health capacity to respond to emerging infectious diseases, the declining rate of autopsies performed in US hospitals reduces the possibility of early detection of such diseases (*9*). Because most autopsies in the United States are now performed by medical examiners and coroners (*10*), medicolegal death investigation system–based surveillance for unexplained death can serve as a sentinel system to identify new agents, recognize unique characteristics of known pathogens, or detect acts of bioterrorism (*11*). Medical examiner and coroner systems contribute to national mortality data and autopsy-based information (*12*), and specimens collected at autopsy of persons whose deaths are unexplained could lead to diagnoses from advancements in diagnostic methods that have enabled identification and characterization of new infectious agents.

Although an earlier study measured unexplained deaths and critical illnesses (*4*), the demographic characteristics and clinicopathologic syndromes of persons whose deaths are unexplained who undergo autopsies have not been described. Understanding the types of persons who died of unexplained causes and who undergo autopsies might help identify specimens for diagnostic testing and improve epidemiologic and mortality data. We analyzed demographic characteristics and infectious disease–related syndromes associated with unexplained death in decedents for whom an autopsy was performed in the United States.

Methods

Data Source and Study Population

We obtained multiple cause-of-death data with autopsy status for 2003–2006 in the 50 states and the District of Columbia from the National Center for Health Statistics

(NCHS), Centers for Disease Control and Prevention (*13*). Multiple cause-of-death data contain information from all death certificates for US residents, including demographic information and causes of death that have been translated to International Classification of Diseases, 10th Revision (ICD-10), codes (*14*).

On the basis of the previous definition of unexplained death (*15*) that was refined to use ICD-10 codes, we used 99 codes likely to represent deaths from unexplained infectious causes to select decedents for this study (online Appendix Table, wwwnc.cdc.gov/EID/article/18/4/11-1311-TA1.htm). These codes aimed to capture deaths from infectious causes that lacked an identifiable etiologic agent or deaths with unknown causes. Unexplained deaths were defined as deaths of previously healthy US residents 1–49 years of age for whom the death certificate had ≥1 codes for unexplained infections. Decedents with unexplained infections for whom any of the ICD-10 codes listed in the Table 1 as an underlying cause of death were not considered previously healthy and were excluded from analysis. Decedents outside the age range also were excluded. We excluded infants (<1 year of age) to eliminate deaths attributed to congenital problems and persons ≥50 years of age because of the expected increased proportion of unexplained deaths from noninfectious causes (*15*). Analyses were restricted to unexplained deaths for which we could ascertain from the selected death certificate data whether an autopsy had been performed.

Study Measures and Statistical Analysis

Decedents were described by age, sex, and race and by the syndromic category recorded on the death certificate. Age was categorized as 1–17 years (children), 18–39 years, and 40–49 years. Race categories were white, black, and other, as recorded on death certificates and obtained from NCHS (*13*). Death certificates enabled reporting of ≥1 race, including any combination of white, black or African

Table 1. Excluded ICD-10 codes and cause-of-death categories for unexplained deaths possibly resulting from infectious causes, United States, 2003–2006*

ICD-10 code	Cause-of-death category
B20-B24	HIV disease
C00-D48	Neoplasms
D73 (except D73.3)	Diseases of spleen
D80-D89	Certain disorders involving immune mechanism
E10-E14	Diabetes mellitus
F02.4	Dementia in HIV disease
R75	Inconclusive laboratory evidence of HIV
S00-T98	Injury, poisoning and certain consequences of external causes
V01-V99	Transport accidents
W00-X59	Other external causes of accidental injury
X60-X84	Intentional self-harm
X85-Y09	Assault
Y10-Y34	Event of undetermined intent
Y40-Y84	Complications of medical and surgical care

*ICD-10, International Classification of Diseases, 10th Revision.

American, American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander, and decedents were imputed to a single race according to their combination of races, Hispanic origin, sex, and age indicated on the death certificate (*16*). On the basis of the selected ICD-10 codes, unexplained deaths were also grouped into 6 clinicopathologic syndromes: gastrointestinal, neurologic, respiratory, cardiovascular, sepsis/shock, and unknown/other (Table 2). Unexplained deaths for which ICD-10 codes were recorded as belonging to ≥2 syndromic categories were classified as multisyndrome.

We calculated odds ratios (ORs) with 95% CIs for selected characteristics by using logistic regression analysis. Characteristics considered univariately associated (p<0.1) with autopsy were further assessed through multivariate logistic regression models to determine which variables were independently associated with autopsy. We considered p<0.05 as significant. Because of the large sample size, statistical but not meaningful significance was found for most variables in the logistic regression model, including all unexplained deaths during 2003–2006 (data not shown). To further evaluate the variables, we created a multivariate logistic regression model using unexplained death data from Arizona for 2003–2006 (*17*). This subset of data was selected because of the minimal amount of missing autopsy data (0.2%) and the Unexplained Deaths Investigation Protocol, which identifies deaths that might be of public health concern, established by the Arizona Department of Health Services (*18*).

Results

United States

A total of 153,476 deaths were reported for persons 1–49 years of age for whom the selected ICD-10 codes (online Appendix Table) were recorded in the multiple cause-of-death data for 2003–2006. Of these, 111,160 (72.4%) met the definition for unexplained death, and information on autopsy status was available for 96,242 (86.6%). Of decedents for whom autopsy status was known, 38,332 (39.8%) had undergone autopsy.

Of decedents for whom autopsy status was known, 59.5% were male (Table 3). Most decedents whose deaths were unexplained (55.1%) were 40–49 years of age; children accounted for 9.2%. Whites composed 71.7% of unexplained deaths, followed by blacks (24.6%) and others (3.7%). For most unexplained deaths, cause was coded as unknown/other syndrome (33.1%). Sepsis/shock accounted for 21.6%, and gastrointestinal and neurologic causes accounted for only 1.8% each.

More male than female decedents underwent autopsies (41.5% vs. 37.4%) (Table 3). The highest percentage of autopsies was performed for white decedents (40.7%);

Table 2. Syndromic classification of selected ICD-10 codes and cause of death for unexplained deaths possibly resulting from infectious causes, United States, 2003–2006*

Syndrome	ICD-10 codes
Gastrointestinal	A04.9, A05.9, A07.9, A08.4, A09, B82.0, B82.9, K29.7, K29.9, K51.9, K65.9, K85.9, R11, R85.5, R85.6, R85.7
Neurologic	A81.9, A83.9, A84.9, A85.2, A86, A87.9, A89, A92.9, A94, G00.9, G03.9, G04.9, G06.2, R29.8, R40.2, R83.5
Respiratory	J01.9, J02.9, J03.9, J06.9, J12.9, J15.9, J18.0, J18.1 J18.2, J18.8, J18.9, J20.9, J21.9, J22, R04.9, R84.5, R84.6, R84.7
Cardiovascular	D59.4, D59.9, D61.9, D64.9, D69.6, I01.9, I30.9, I33.9, I40.9, I42.8, I42.9, I51.4, I77.6, L95.9
Unknown/other	A28.9, A49.8, A49.9, A64, A68.9, A99, B09, B34.9, B49, B64, B83.9, B88.9, B89, B94.9, B99, D73.3, M60.0, N10.9, O98.9, P36.9, P37.9, P39.9, P50.9, R56.8, R59.9, R69, R89.5, R89.6, R89.7, R96.0, R96.1, R98, R99
Sepsis/shock	A41.9, R57.9
*ICD-10, International Classification of Diseases, 10th Revision.	

autopsies were performed for 38.1% of black decedents and 34.0% of other decedents. Children whose deaths were unexplained underwent the highest percentage of autopsies (50.5%), followed by persons 18–39 years (48.4%) and 40–49 years of age (32.5%). The highest percentage of autopsies were performed on decedents whose cause of death was coded as unknown/other syndrome (65.3%); the lowest percentage of autopsies were performed on decedents whose deaths were coded as sepsis/shock syndrome (15.9%).

Table 3. Characteristics of decedents 1–49 years of age and autopsies conducted for unexplained deaths possibly resulting from infectious causes, United States*

Characteristic	No. (%) decedents	No. (%) autopsies
Overall	96,242 (100)	38,332 (39.8)
Sex		
M	57,238 (59.5)	23,753 (41.5)
F	39,004 (40.5)	14,579 (37.4)
Race		
White	69,053 (71.7)	28,125 (40.7)
Black	23,657 (24.6)	9,006 (38.1)
Other†	3,532 (3.7)	1,201 (34.0)
Age group, y		
1–17	8,844 (9.2)	4,468 (50.5)
18–39	34,382 (35.7)	16,640 (48.4)
40–49	53,016 (55.1)	17,224 (32.5)
Syndrome		
Gastrointestinal	1,736 (1.8)	837 (48.2)
Neurologic	1,765 (1.8)	676 (38.3)
Respiratory	15,229 (15.8)	5,607 (36.8)
Cardiovascular	12,487 (13.0)	4,404 (35.3)
Sepsis/shock	20,762 (21.6)	3,298 (15.9)
Multisyndrome	12,371 (12.9)	2,688 (21.7)
Unknown/other	31,892 (33.1)	20,822 (65.3)

*Numbers reflect decedents for whom autopsy information was available; autopsy information was not available for 13.4% of the 111,160 persons who died of unexplained causes.
†American Indian or Alaska Native, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, Native Hawaiian, Guamanian or Chamorro, Samoan, other Pacific Islander, and other.

Arizona

Of the 2,097 persons in Arizona who died from unexplained possibly infectious causes and for whom autopsy status was known, most (55.2%) were 40–49 years of age (Table 4). Whites composed 78.6% of such decedents, followed by others (14.4%) and blacks (7.1%). Most (33.9%) unexplained deaths resulted from unknown/other causes; unexplained deaths from gastrointestinal causes accounted for 1.2%.

Percentages of decedents for whom an autopsy was performed were similar for whites (35.2%) and blacks (35.8%) (Table 4). The highest percentages of autopsies were performed on children whose deaths were unexplained (44.5%), followed by persons 18–39 years (38.0%) and 40–49 (28.1%) years of age. Of the 7 syndromic classifications, gastrointestinal cause of death accounted for the highest percentage of autopsies (60.0%) and sepsis/shock for the lowest percentage (14.5%).

Univariate analysis of data on persons who died from unexplained infectious causes in Arizona indicated that race, age group, and syndromic category, but not sex, were significantly associated with autopsy. Multivariate logistic regression analysis indicated that race, age group, and syndromic category remained independent predictors of autopsy. Persons of other races were less likely than white persons to undergo autopsy (OR 0.5, 95% CI 0.4–0.7) (Table 4). Children whose deaths were unexplained (OR 1.9, 95% CI 1.4–2.6) and persons 18–39 years of age (OR 1.6, 95% CI 1.3–2.0) were more likely to have undergone autopsy than were persons 40–49 years of age (Table 4). Persons with cardiovascular conditions, sepsis/shock, and multisyndrome conditions were less likely to have undergone autopsy than were persons with unknown/other unexplained deaths (Table 4).

Discussion

Unlike other studies that have described and analyzed characteristics that influence autopsies overall (19,20), ours describes demographic characteristics and clinicopathologic syndromes associated with autopsy of persons who died of unexplained infectious causes in the United States. The overall percentage of autopsies performed on such decedents during 2003–2006 (39.8%) was higher than estimates of the proportion of overall autopsies in the United States (≈8.5%) (21). The higher percentage of autopsies for persons whose deaths were unexplained might reflect the frequent inclusion of complete autopsies in investigations of natural disease deaths by medical examiners and coroners (22).

Our finding that most characteristics in the multivariate regression analysis were highly significant when complete data for 2003–2006 were included in the analysis probably resulted from the large number of persons in the study whose deaths were unexplained. Unexplained deaths among persons with a history of fever have been reportable in Arizona since 2004, and medical examiners and health care providers are required to report these unexplained deaths to their local health departments (18). The Arizona Unexplained Deaths Investigation Protocol identifies appropriate specimens and clinical data needed for investigation, and the Arizona data might elucidate true demographic characteristics and syndromic trends of unexplained deaths in the United States. The analysis of data for Arizona decedents suggests that race, age, and clinicopathologic syndrome are potentially major factors for whether persons who died of unexplained infectious causes undergo autopsy.

Data on religious preferences are not collected on death certificates, but race might have been a proxy for

Table 4. Association between having undergone autopsy and demographic characteristics of decedents 1–49 years of age and clinicopathologic syndrome for unexplained deaths possibly resulting from infectious causes, Arizona, USA*

Characteristic	No. (%) decedents	No. (%) autopsies	Adjusted odds ratio (95% CI)
Total	2,097 (100.0)	696 (33.2)	
Race			
White	1,648 (78.6)	580 (35.2)	Reference
Black	148 (7.1)	53 (35.8)	1.0 (0.7–1.5)
Other†	301 (14.4)	63 (20.9)	0.5 (0.4–0.7)
Age group, y			
1–17	211 (10.1)	94 (44.5)	1.9 (1.4–2.6)
18–39	728 (34.7)	277 (38.0)	1.6 (1.3–2.0)
40–49	1,158 (55.2)	325 (28.1)	Reference
Syndrome			
Gastrointestinal	25 (1.2)	15 (60.0)	1.8 (0.8–4.1)
Neurologic	54 (2.6)	28 (51.9)	1.2 (0.7–2.1)
Respiratory	319 (15.2)	142 (44.5)	0.9 (0.7–1.2)
Cardiovascular	213 (10.2)	59 (27.7)	0.4 (0.3–0.6)
Sepsis/shock	428 (20.4)	62 (14.5)	0.2 (0.2–0.3)
Multisyndrome	348 (16.6)	56 (16.1)	0.2 (0.2–0.3)
Unknown/other	710 (33.9)	334 (47.0)	Reference

*By multivariate logistic regression analysis. Numbers reflect decedents for whom autopsy information was available; autopsy status was not available for 0.2% of the 2,102 persons who died of unexplained causes. Variables are independently associated with autopsy.
†American Indian or Alaska Native, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, Native Hawaiian, Guamanian or Chamorro, Samoan, Other Pacific Islander, and Other.

cultural and religious preferences. Religious objections and lack of understanding about cultural or religious influences have been reported as reasons a family might not consent to an autopsy (*23,24*). For example, many American Indian tribes have traditions contrary to autopsy in which organ specimens are retained by medical examiners and pathologists (*25*). The observed lower odds for autopsy of decedents of other races possibly resulted from the larger American Indian population in Arizona (5%) than in the United States (1%) (*26*).

Results from the analysis of the Arizona subset suggest that children and young adults whose deaths resulted from unexplained possibly infectious causes are more likely than older adults to have undergone autopsies. Although some studies have suggested that children are more likely to undergo autopsies (*19,20*), the literature regarding the association between age and autopsy is limited, and findings have been inconclusive (*27,28*). Particularly when children die suddenly or unexpectedly, which is often from infectious causes (*29*), autopsies can contribute to families' understanding of the circumstances of death or expand medical knowledge (*19,30*).

Persons whose unexplained deaths were coded as from cardiovascular, sepsis/shock, or multisyndrome causes were less likely than those whose deaths were coded as unknown/other to undergo autopsies. These results could reflect differences in the availability and resources of investigators of unexplained deaths from possibly infectious causes. Sepsis, in particular, remains perplexing and costly, and despite efforts to understand the systemic inflammation and multisystem organ failure characteristics of severe sepsis, the reason many of these patients die remains unknown (*31,32*). Furthermore, investigators of unexplained deaths or family members of decedents might have believed that additional studies, including autopsy, would not yield substantial findings. According to an opinion survey of pathology and medicine resident physicians, reasons families refuse autopsies included beliefs that the patient has suffered enough and that the autopsy would not be useful (*33*). Routine microscopic examination has been argued to not provide additional information in forensic pathology cases for which the cause and manner of death are apparent at the time of autopsy (*34*). However, the reduced likelihood of autopsy or further evaluation of these challenging unexplained deaths could also result in the failure to recognize infectious diseases. For example, Chong et al. illustrated the difficulty of differentiating an emerging disease (SARS) from other causes of sudden cardiovascular death at autopsy (*35*). Of the14 autopsies performed on persons with suspected or probable SARS, 8 confirmed SARS only on the basis of clinical history, histopathologic evaluation, and testing of autopsy specimens. Therefore, an autopsy should be pursued especially for those whose unexplained deaths were possibly of infectious causes.

Reasons for differences in likelihood of autopsy with respect to race, age, and clinicopathologic syndrome could be multifactorial, and results from our study are subject to limitations. The availability, training, and resources of investigators of unexplained natural deaths differ among institutions and jurisdictions and might account for differences in autopsy performance, testing capabilities, and reporting of autopsy data (*12,36*). Unfortunately, multiple cause-of-death data do not capture whether autopsies are performed by medical examiners or by hospital-based pathologists, and differences in autopsy rates between medicolegal death investigation systems and hospital-based pathologists in unexplained death remains unknown. Inaccuracy in death certification and reliance solely on ICD-10 classification for unexplained death also has limitations. Codes might be assigned by persons not directly familiar with decedents and who therefore might not be aware of known diagnoses. Death certificates might not have been amended when organism-specific etiologies (i.e., *Streptococcus pneumoniae*) were determined after broad ICD-10 codes (i.e., bacterial meningitis) were assigned. Results from our study also are limited by the restriction of analyses to unexplained deaths for which autopsy status is known and the large variation of autopsy data reported by states to NCHS. Of deaths that met the unexplained death definition, the percentage of missing autopsy status data by state ranged from 0 to 99% during 2003–2006. Additional data on autopsy status reported to NCHS could have more accurately described unexplained death.

Additional studies are needed to assess the similarities in demographic characteristics and clinicopathologic syndromes of persons who died of unexplained possibly infectious causes and characteristics found in autopsies overall. The statistically significant findings of such characteristics as age and race in this study could reflect general trends of autopsies performed and might not be unique to persons whose infectious deaths are unexplained. Furthermore, results from the analysis of Arizona data might not necessarily reflect unexplained deaths in other states or nationally.

Additional insight into persons who died of unexplained infectious causes and underwent autopsies might help pinpoint areas in which diagnostic capabilities or resources are needed (*15*) and provide opportunities for additional studies. Retrospective studies using postmortem specimens and improved diagnostic tools could benefit the broader community. Improved understanding by health departments and medical examiners of a specific type of unexplained death for which an autopsy is conducted could increase overall awareness of unexplained deaths from

infectious causes; improve approaches in the collection of medical history and laboratory results in the forensic setting (*37*); and strengthen collaboration between health departments, clinicians, and medical examiners. Awareness of the types of unexplained death for which autopsies are less likely to be conducted is also imperative. Clinicians and pathologists challenged by cultural or religious restrictions can consider alternative methods for diagnosis such as taking biopsy samples (*38*), collecting appropriate antemortem specimens, or performing virtual autopsies (*39,40*). Retrospective studies evaluating perceptions by families, physicians, and medical examiners on autopsies of persons who died of unexplained infectious causes also might be helpful. Improving education about unexplained death and autopsy, identifying areas where diagnostic resources are needed, and maintaining cooperation between investigators should be considered. Autopsy findings, in conjunction with clinical history and diagnostic tools, can assist surveillance and investigations of infectious diseases of public health concern.

Acknowledgments

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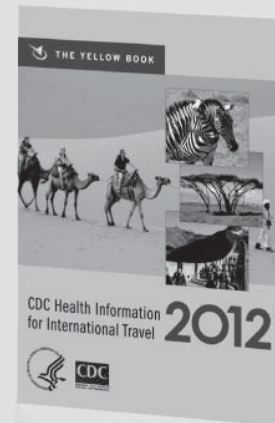
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