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Cryptosporidiosis in the Elderly Population of the United States

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Abstract

Background—Although cryptosporidiosis has been a nationally notifiable disease since 1995, surveillance estimates are undermined by limited diagnostic testing and incomplete reporting of cases to health authorities. Further, existing surveillance systems do not capture the specific risks of cryptosporidiosis to sensitive populations, such as the elderly population. The Centers for Medicare and Medicaid Services databases present a novel means to investigate the cryptosporidiosis burden in the US elderly population.

Methods—We abstracted records for all Medicare-covered persons aged ≥ 65 years who received a diagnosis of a cryptosporidiosis-related illness between 1991 and 2004 ($n = 1304$) in the United States. Annual rates of cryptosporidiosis-related hospitalization were calculated and compared with surveillance data published by the Centers for Disease Control and Prevention. The total burden of disease and outcomes of hospitalization were also assessed.

Results—Cryptosporidiosis-related hospitalizations increased during the study period at a rate of 0.15–0.39 cases per 100,000 elderly persons each year; this increase was probably attributable to increased awareness and testing. Comparison between cryptosporidiosis-related hospitalization and Centers for Disease Control and Prevention surveillance data revealed considerable state-to-state variation. The rate of hospitalization among persons aged ≥ 85 years was more than double that among persons aged 65–74 years. Volume depletion and noninfectious diseases of the digestive system were common concurrent diagnoses. The highest case-fatality rates were among persons aged ≥ 85 years (7.8%) and among persons infected with HIV (10.3%).

Conclusions—Although awareness of cryptosporidiosis has increased, underdiagnosis and underreporting of cases remains a major barrier to accurate surveillance in many states. Infection among elderly persons is associated with volume depletion and negative hospital outcomes, including death.

Cryptosporidium is an important cause of gastrointestinal illness, particularly among immunocompromised persons. The elderly may be especially sensitive to cryptosporidiosis [1,2], although few studies have specifically assessed the burden of infection in this population. In the United States, cryptosporidiosis has been a nationally notifiable disease since 1995. State health departments report cases of cryptosporidiosis to the Centers for Disease Control and

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Prevention (CDC) on a weekly basis. Since 1998, the reported annual rate of cryptosporidiosis among persons aged ≥ 65 years varied between 0.29 and 0.70 cases per 100,000 population. Surveillance inherently identifies a minimum number of cases, because reporting to the CDC is not mandatory, and the decision to make a disease notifiable is made by each state. In addition, existing mechanisms for waterborne disease surveillance do not address the specific risks to sensitive populations, such as the elderly population [3].

Surveillance estimates of cryptosporidiosis are also undermined by the limited use of diagnostic tests. For instance, of 32,408 specimens evaluated for ova and parasites in Connecticut during 1994, only 1714 (5.3%) were tested for *Cryptosporidium* [4]. Of 83 *Cryptosporidium*-positive samples, only 10 were reported to state health authorities. In 2000, fewer than 11% of FoodNet laboratories routinely included *Cryptosporidium* testing as part of ova and parasites exams, unless specifically requested by the health care provider [5]. The situation is not very different today (J. Jones, personal communication), and the extent to which underdiagnosis and nonreporting of cases continues to affect surveillance estimates is unknown.

The Centers for Medicare and Medicaid Services (CMS) databases present a novel means to investigate the burden of cryptosporidiosis among elderly persons in the United States, because they include information on all hospitalized Medicare beneficiaries nationwide. These records include information on ~96% of the US elderly population [6]. We sought to describe trends in hospitalization, demographic characteristics, and temporospatial characteristics of cryptosporidiosis among elderly persons in the United States with use of CMS databases. We also contrasted estimates of the burden of cryptosporidiosis derived from the CMS databases with those published by the CDC.

METHODS

Hospitalization records

All records for persons aged ≥ 65 years containing codes for gastrointestinal disease were extracted from the CMS Medicare Provider Analysis and Review database for a 14-year period (1 January 1991 through 31 December 2004). Patient age, sex, race, place of residence (by zip code), date of admission and discharge, discharge destination, and up to 10 diagnostic codes (classified by the International Classification of Disease, 9th edition, with Clinical Modification [ICD-9-CM]) were available for each record. Because the ICD-9-CM code for cryptosporidiosis (007.4) was not introduced until October 1997, we abstracted all records containing this code as well as those for cryptosporidiosis-like illnesses, including coccidiosis (007.2), other specified protozoal disease (007.8), and unspecified protozoal disease (007.9). Unless otherwise noted, the term cryptosporidiosis-related hospitalization or cryptosporidiosis-related illness denotes the total number of records containing ICD-9-CM codes 007.2, 007.4, 007.8, or 007.9. All records that contained these codes in any 1 of the 10 diagnostic fields were included in the analysis.

To assess the total burden of disease among persons with cryptosporidiosis-related illness, all ICD-9-CM codes from the subset of records containing this diagnosis were abstracted. We aggregated codes by the major groupings in the ICD-9-CM Tabular List of Diseases and Injuries, which are based on the body system affected or disease etiology. In addition, we abstracted specific codes for conditions that may predispose a patient to or arise as a complication of cryptosporidiosis-related illness or that may otherwise influence diagnosis and patient outcome. Because of changing nosological practices during the period studied, the case definition for HIV infection was expanded to include AIDS, AIDS-related complex, and other HIV disease (codes 042–044), HIV-2 infection (079.53), deficiency of cell-mediated immunity (279.19), inconclusive HIV test results (795.91 or 795.8), and asymptomatic HIV infection (V08) [7]. Severity of cryptosporidiosis-related illness was assessed using duration of stay and

discharge destination information. Records were limited to the 50 US states and the District of Columbia to better match the reports available from the CDC. This research was reviewed and exempted by the institutional review board at Tufts University School of Medicine. Data presented in table 1 was reviewed and approved by CMS.

CDC surveillance reports

The annual number of cryptosporidiosis cases was obtained from the Summary of Notifiable Diseases for the United States, which is published annually in the public domain in the Morbidity Mortality Weekly Report of the CDC [8]. The annual number of cases was available for persons of all ages and for persons aged ≥ 65 years, at the state and national level, respectively. Surveillance data were obtainable beginning in 1997. Continuous time series spanning the period 1997–2004 were not available for Alabama, Connecticut, Hawaii, Idaho, North Carolina, Pennsylvania, Virginia, and Washington, because cryptosporidiosis was not notifiable in these states during all years of this period.

Census data

National data on age, sex, and race/ethnicity for all persons aged ≥ 65 years were abstracted from the 1990 and 2000 Decennial Census. The number of persons in the overall and the elderly population were also abstracted by state. Annual estimates for these populations were derived by linear interpolation between Census years. Annual rates of cryptosporidiosis-related hospitalization events per 100,000 elderly persons were calculated using the mean elderly population count as the denominator. Denominators were adjusted for age, race, sex, and state, where appropriate. Surveillance counts of cryptosporidiosis were similarly converted into rates using the mean total population by state as the denominator.

Data analysis

Data abstraction and analysis was performed using SAS, version 9.1 (SAS Institute), and SPSS, version 16.0 (SPSS). Maps were created using ArcGIS, version 9.2 (ESRI).

RESULTS

Temporal and spatial trends

A total of 1304 records with a diagnosis of cryptosporidiosis-related illness were identified among persons aged ≥ 65 years. The rate of hospitalizations increased steadily after the code for cryptosporidiosis (007.4) was introduced in 1997 (figure 1). Among 178 cryptosporidiosis-related hospitalizations in 1993, 116 (65.2%) involved patients from Wisconsin, of which 106 (91.4%) were from Milwaukee. Eighty-five (80.2%) of these 106 patients were hospitalized during a well-documented outbreak that occurred from 28 March through 24 April 1993 [10].

The annual rates of cryptosporidiosis-related hospitalization among elderly persons and rates of reported cryptosporidiosis in the total population varied considerably by state (figure 2). In Wisconsin, the CDC estimate for the annual rate of cryptosporidiosis in the total population was ~6 times the rate in the elderly inpatient population. Maine, Montana, North Dakota, and Vermont showed particularly high rates of reporting in the total population relative to the rate among elderly in-patients. The cryptosporidiosis-related hospitalization rate among elderly inpatients exceeded the rate reported for the total population in Alaska, Arizona, and West Virginia. Disparity also existed in the use of the cryptosporidiosis-specific ICD-9-CM code between states (figure 3).

Demographic trends

The annual rate of cryptosporidiosis-related hospitalization was similar among men and women (table 1), although comparative rates by sex varied by up to 50% by year (not shown). Cryptosporidiosis-related hospitalization rates increased with age for both sexes; the rate among persons aged ≥ 85 years was more than double that among persons aged 65–74 years. This positive trend of cryptosporidiosis-related hospitalization with age persisted when rates were stratified by race, although the number of cases among non-white individuals was too small to make statistical inferences.

Total burden of disease

Cryptosporidiosis-related illness accounted for a small fraction of the disease burden in the subset of records containing this diagnosis (figure 4A). However, cryptosporidiosis-related illness was the most common primary diagnosis in such records, accounting for 35.3% of codes listed in the first diagnostic field. A median of 6 additional codes (range, 0–9 codes) were included in each record; selected concurrent diagnoses are shown in figure 4B. Fifty-eight records contained a diagnosis of HIV/AIDS. These admissions were more likely to have occurred before 1996 (OR, 2.8; 95% CI, 1.7–4.6; $P < .001$). Infection with at least 1 other enteric pathogen was reported in 137 records. Cryptosporidiosis-related illness was the primary diagnosis in 16% of such records, whereas 35% listed an alternate infection as the primary diagnosis. *Clostridium difficile* and *Giardia lamblia* accounted for 42% and 15% of other enteric pathogens identified, respectively. Noninfectious diseases of the digestive system were also common in this population; intestinal obstruction and diverticulosis/diverticulitis of the intestine (codes 560 and 562; 31.0%) and noninfectious enteritis/colitis (codes 555 and 558; 17.2%) were the most common diagnoses relating to the digestive system. Volume depletion was the most common concomitant diagnosis; volume depletion occurred with similar frequency among persons with and without HIV/AIDS (OR, 1.56; 95% CI, 0.9–2.6; $P = .095$) or malignancy (OR, 0.89; 95% CI, 0.6–1.2; $P = .503$).

Outcome of hospitalization

Duration of hospitalization varied between 1 and 169 days. Median duration of stay was longer among persons aged ≥ 85 years, compared with persons aged 65–74 years (8 vs. 6 days; $P < .001$) and with persons aged 75–84 years (8 vs. 7 days; $P = .004$). The median duration of stay was not different when records were stratified by HIV/AIDS status (7.5 and 7 days among HIV-positive and HIV-negative persons, respectively; $P = .269$) or by presence/absence of malignancy (10.5 and 11 days among persons with and without malignancy, respectively; $P = .108$).

Discharge to home was reported for 59.9% of records (768 of 1304 records) and was more common in records that did not contain a diagnosis of HIV/AIDS (59.5% among HIV-negative and 46.6% among HIV-positive individuals; $P = .051$). Discharge to home was less common among persons aged 75–84 years (61.7%) and ≥ 85 years (35.5%), compared with persons aged 65–74 years (69.0%; $P = .014$ and $P < .001$, respectively). Younger age category (OR, 2.1; 95% CI, 1.8–2.4; $P < .001$) and HIV seronegativity (OR, 2.88; 95% CI, 1.7–5.0; $P = .001$) were highly significant predictors of discharge to home in multivariate models.

In-hospital death was reported in 5.4% of records (71 of 1304 records), only 20% of which listed cryptosporidiosis-related illness as the primary diagnosis. The highest case-fatality rate occurred among persons aged ≥ 85 years (7.8%) and among persons with HIV/AIDS (10.3%). In-hospital death was more common among persons with HIV/AIDS who were admitted prior to 1996 (12.1% vs. 8.0%), although this assessment was limited by small sample size.

DISCUSSION

We observed a positive trend in cryptosporidiosis-related hospitalization from 1991 through 2004 among persons aged ≥ 65 years. A similar trend was documented in CDC surveillance reports for this age group. *Cryptosporidium* can be waterborne, and the true incidence of waterborne illness may be increasing in association with an aging population that is particularly vulnerable [11]. However, the upward trend in cryptosporidiosis-related hospitalizations contrasted with the decrease in *Giardia*-related hospitalizations during this period (figure 5; online only), which suggests that increased awareness and testing, rather than increased incidence, may account for the positive trend in cryptosporidiosis-related hospitalization. The growing use of more-sensitive diagnostic tests, such as direct antigen and nucleic acid detection, may have contributed to this trend. Unfortunately, data on laboratory practices spanning this period are limited. In 2000, 53% of laboratories in FoodNet states were using the less sensitive acid-fast staining method to make the diagnosis of cryptosporidiosis [5].

The peak in coccidiosis (code 007.2) during the 1993 Milwaukee outbreak and the continued high use of this code in some states subsequent to the introduction of the specific code for cryptosporidiosis, suggests issues with regard to coder awareness. Coccidiosis is a term that refers to a number of coccidian infections, including cryptosporidiosis. Confusion may arise, because this code (007.2) is intended to be used only for *Isospora* infection. Isosporiasis shares a similar epidemiology with and is clinically akin to cryptosporidiosis, but it is a far less common cause of waterborne illness [12]. We believe that the great majority of coccidiosis cases in these records are actually cryptosporidiosis. This view is supported by the finding that in Wisconsin, a state that has enhanced awareness of cryptosporidiosis after the 1993 outbreak, 92.5% of records examined during the study period contained a specific diagnosis of cryptosporidiosis (007.4).

The rate of cryptosporidiosis-related hospitalization increased with age, with the highest incidence observed among persons aged ≥ 85 years. This trend was true across all sex and race categories and confirms our previous findings [10]. Because surveillance data published by the CDC are aggregated for persons aged ≥ 65 years, it is unclear if this trend exists among cases reported to the CDC. The higher rate of cryptosporidiosis-related hospitalization among the oldest individuals may reflect a true increase in cryptosporidiosis incidence, perhaps attributable to age-related immune senescence or increased exposure arising from lifestyle changes peculiar to this subpopulation (e.g., communal living in nursing homes) [13]. More likely, the oldest individuals may experience more-severe illness because of dehydration and other complicating factors and, thus, are at increased risk of hospitalization.

Other enteric infections were reported in ~10% of records containing a diagnosis of cryptosporidiosis-related illness. Coinfection with *C. difficile* and *Cryptosporidium* has been reported elsewhere among elderly patients [2]. We found that other infections, such as infection due to *Giardia* and enteric bacteria, were twice as likely to be listed as the primary diagnosis, compared with cryptosporidiosis-related illnesses. The nosological practice of deferring to an admission diagnosis may partly account for this discrepancy, because a diagnosis of cryptosporidiosis may not be sought until later in the hospitalization, when other pathogens have been ruled out. We also speculate that these other infections may be prioritized for billing purposes, because they have well-defined treatment guidelines. Prior to the approval of nitazoxanide in 2005, supportive therapy was the only means available to treat cryptosporidiosis in adults. Moreover, cryptosporidiosis is generally considered to be a self-limiting infection in immunocompetent individuals.

Noninfectious conditions of the digestive tract were common among persons with cryptosporidiosis-related illness. The high incidence of some conditions, such as diverticular

disease, might be expected in this elderly population, unrelated to cryptosporidiosis. Elderly patients likely undergo a barrage of tests, and cryptosporidiosis may be an incidental finding in at least some patients. Diagnostic workup during an acute episode of cryptosporidiosis may also lead to the detection of other non-infectious conditions. Further, admission signs and symptoms ascribed to a noninfectious gastrointestinal condition may subsequently be demonstrated to be attributable to cryptosporidiosis. At least 1 study has found that cryptosporidiosis can mimic and exacerbate inflammatory bowel diseases, such as Crohn's disease [14]. Studies performed in animals have also found that *Cryptosporidium* can induce and accelerate the development of lesions similar to those found with inflammatory bowel diseases [15,16]. Unfortunately, given the nature of CMS records, it was not possible to ascertain the relative timing of onset and detection of cryptosporidiosis and inflammatory bowel diseases in this study.

Cryptosporidium is a well-recognized cause of diarrhea, dehydration, and volume depletion, particularly in sensitive populations [17]. We found that more than two-thirds of records that contained a diagnosis of cryptosporidiosis-related illness also reported volume depletion. Elderly persons may be particularly prone to hospitalization as a result of this complication because of coexisting conditions, such as congestive heart failure and renal disease, which can be aggravated by fluid and electrolyte imbalances due to diarrhea and its treatment. Thus, cryptosporidiosis may contribute substantially to poor outcomes, even when it is not considered the primary reason for hospitalization.

Immune system compromise attributable to cancer chemotherapy or HIV infection is a well-recognized risk factor for cryptosporidiosis. Diabetes and pulmonary diseases treated with steroids are also relatively immunosuppressed conditions [18], and were among the more common concurrent diagnoses in this study. In the United States, malignancy is the second-most common discharge diagnosis among persons aged ≥ 65 years, occurring at a rate of 22 cases per 1000 population [19]. We found a higher rate of malignancy among persons hospitalized with cryptosporidiosis-related illness (130 cases per 1000 records). However, to capture records from all patients with cancer, we included codes in up to 10 diagnostic fields; the national estimate of 22 cases per 1000 population was derived from only primary diagnoses. Malignancy was the primary diagnosis in only 18.8% of records (32 of 170 records) that contained this diagnosis in our study. Presumably, cancer chemotherapy predisposed some of these patients to cryptosporidiosis-related illness. We found no evidence to suggest that persons with a malignancy were more likely to develop severe disease.

Few reports of cryptosporidiosis among elderly HIV-infected patients exist in the literature. In 1 elderly person, the detection of *Cryptosporidium* in a stool specimen led to an unsuspected diagnosis of HIV infection at an age of 68 years [20]. Because people with HIV/AIDS are living to an older age in the United States, knowledge of the manifestations and outcomes of opportunistic infections will become increasingly important in this cohort. We identified 58 records that contained a diagnosis of HIV/AIDS and cryptosporidiosis-related illness. These patients were less likely to be discharged to home and had a higher in-hospital mortality rate. Unfortunately, it was not possible to identify who among these patients was receiving antiretroviral therapy and when such treatment was initiated. We did, however, find evidence that both the incidence of and the mortality associated with cryptosporidiosis-related illness was higher in the years prior to the widespread introduction of antiretroviral drugs in 1996. This trend has been documented elsewhere for other opportunistic infections [21]. The relatively high rate of HIV/AIDS noted in this study (44 cases per 1000 records), compared with the general elderly population (0.12 cases per 1000 population in 1998 [22]), may reflect an enhanced rate of testing for cryptosporidiosis among HIV-infected patients, as well as an increase in HIV screening among persons diagnosed with cryptosporidiosis.

CMS databases are the most complete records available for studying cryptosporidiosis incidence in the US elderly population. Because records are generated for billing purposes, they are not subject to many of the biases associated with public health reporting. Unlike national surveillance data, specific information is available on the demographic and clinical characteristics of persons with cryptosporidiosis-related illness. However, there are some limitations. Clearly, cases involving hospitalized patients represent the tip of the iceberg in terms of true cryptosporidiosis incidence. It is not possible to determine who among the total elderly population is hospitalized with cryptosporidiosis using these records. However, because virtually all persons aged ≥ 65 years are eligible for Medicare, sociodemographic factors, such as age and income, should not be a significant barrier to health care and testing among these persons. The quality of care provided to Medicare beneficiaries varies considerably by state [23], and this may translate into regional differences in the rates of specimen submission and diagnostic testing for *Cryptosporidium*. Because we do not know who among the hospitalized patients underwent testing for cryptosporidiosis and what type of tests were performed, this study does not overcome the important issue of underdetection attributable to not testing and the low sensitivity of diagnostic tests.

This study emphasizes the need for strengthened surveillance systems and increased screening and testing for cryptosporidiosis in the US elderly population. The current system of voluntary reporting of cases vastly underestimates the burden of disease among elderly persons, and lacks sufficient detail to draw conclusions about the importance of infection in this sensitive population. We demonstrate that there is considerable state-to-state variation in awareness of cryptosporidiosis and suggest that testing and reporting practices such as those used in Wisconsin [24] may serve as an example to health practitioners and authorities in all US states.

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Figure 1.

The annual number of cryptosporidiosis-related (CR) hospitalizations derived from Centers for Medicare and Medicaid Services (CMS) databases and reported cases of cryptosporidiosis from the national surveillance program of the Centers for Disease Control and Prevention (CDC) in the US elderly population (persons aged ≥ 65 years) for the period 1991–2004. The breakdown of coding for CR illness is shown. Prior to introduction of the specific code for cryptosporidiosis (007.4) in 1997, it was recommended that infection with this parasite be coded as “other specified protozoal disease” (007.8). Note the frequent use of the code for coccidiosis (007.2) in 1993, corresponding with the Milwaukee outbreak [9].

Figure 2.

Mean annual rate of cryptosporidiosis-related (CR) hospitalization among persons aged ≥ 65 years (from the Centers for Medicare and Medicaid Services databases) versus the mean annual rate of reported cases of cryptosporidiosis in the total population (national surveillance from the Centers for Disease Control and Prevention) for the period 1997–2004. Annual rates have been adjusted for each state to reflect only those years for which surveillance data was available. A, States in which cryptosporidiosis was not a reportable illness for the entire time period are shown in red.

Figure 3. Percentage of Centers for Medicare and Medicaid Services database records that contained a specific diagnosis of cryptosporidiosis (007.4) since the introduction of the code in 1997.

Figure 4.

Total burden of illness among patients aged ≥ 65 years hospitalized with cryptosporidiosis-related (CR) illness in the United States ($n=1304$). *A*, CR illness as a proportion of all diagnoses, by diagnostic field. *B*, selected concurrent diagnoses. Note that records may contain ≥ 1 concurrent diagnosis. The *International Classification of Disease, Ninth Edition, Clinical Modification* codes for each diagnosis listed are: CR illness, 007.2, 007.4, 007.8, 007.9; HIV/AIDS, 042–044, 079.53, 279.19, 795.91, 795.8, V08; renal disease, 403–404, 580–586, V45.1, V56; other enteric infections, 001–009 (excluding 007.2, 007.4, 007.8, 007.9), 120–129; malignancy, 140–208, 230–234; chronic obstructive pulmonary disease (COPD), 490–496; diabetes mellitus, 250; electrolyte imbalance, 276.0, 276.1, 276.7–276.9; heart disease, 391–392.0, 393–398, 402, 404, 410–416, 420–429; noninfectious digestive disease, 520–579; and volume depletion, 276.5.

The figure is available in its entirety in
the online edition of *Clinical Infectious Diseases*.

Figure 5.
(online only). Annual number of cryptosporidiosis-related (CR) hospitalizations and
Giardia-related hospitalizations in the US elderly population for the period 1991–2004.

Age, sex, and race of elderly inpatients with cryptosporidiosis-related illness, abstracted from the Centers for Medicare and Medicaid Services databases.

Table 1

Race and age, years	No. of cases			Annual rate, cases per 100,000 persons aged ≥65		
	Men	Women	Total	Men	Women	Total
All ≥65	519	785	1304	0.27	0.28	0.27
65–74	232	281	513	0.20	0.20	0.20
75–84	210	299	509	0.33	0.30	0.31
≥85	77	205	282	0.48	0.52	0.51
White ≥65	454	709	1163	0.26	0.29	0.28
65–74	195	240	435	0.20	0.20	0.20
75–84	189	275	464	0.33	0.31	0.32
≥85	70	194	264	0.50	0.55	0.53
Black ≥65	38	44	82	0.26	0.19	0.21
65–74	25	22	47	0.27	0.17	0.21
75–84	11	14	25	0.25	0.18	0.21
≥85	2	8	10	0.18	0.27	0.24
Other ≥65	27	32	59	0.29	0.26	0.27
65–74	12	19	31	0.20	0.25	0.23
75–84	10	10	20	0.38	0.27	0.31
≥85	5	3	8	0.77	0.27	0.45