Mortality from selected diseases that can be transmitted by water – United States, 2003–2009

J. W. Gargano, E. A. Adam, S. A. Collier, K. E. Fullerton, S. J. Feinman and M. J. Beach

ABSTRACT

Diseases spread by water are caused by fecal–oral, contact, inhalation, or other routes, resulting in illnesses affecting multiple body systems. We selected 13 pathogens or syndromes implicated in waterborne disease outbreaks or other well-documented waterborne transmission (acute otitis externa, *Campylobacter*, *Cryptosporidium*, *Escherichia coli* (*E. coli*), free-living ameba, *Giardia*, Hepatitis A virus, *Legionella* (Legionnaires' disease), nontuberculous mycobacteria (NTM), *Pseudomonas*-related pneumonia or septicemia, *Salmonella*, *Shigella*, and *Vibrio*). We documented annual numbers of deaths in the United States associated with these infections using a combination of death certificate data, nationally representative hospital discharge data, and disease-specific surveillance systems (2003–2009). We documented 6,939 annual total deaths associated with the 13 infections; of these, 493 (7%) were caused by seven pathogens transmitted by the fecal–oral route. A total of 6,301 deaths (91%) were associated with infections from *Pseudomonas*, NTM, and *Legionella*, environmental pathogens that grow in water system biofilms. Biofilm-associated pathogens can cause illness following inhalation of aerosols or contact with contaminated water. These findings suggest that most mortality from these 13 selected infections in the United States does not result from classical fecal–oral transmission but rather from other transmission routes.

Key words | biofilm, deaths, infections, mortality, outbreaks, waterborne

J. W. Gargano
E. A. Adam (corresponding author)
S. A. Collier
K. E. Fullerton
S. J. Feinman
M. J. Beach
Waterborne Disease Prevention Branch, Division of Foodborne, Waterborne, and Environmental Diseases,
Centers for Disease Control and Prevention,
1600 Clifton Rd NE, MS C-09,
Atlanta,
GA,
USA
E-mail: *eadam@cdc.gov*

S. J. Feinman
Rollins School of Public Health,
Emory University,
Atlanta,
GA,
USA

INTRODUCTION

In the United States, mortality from classic enteric waterborne infections such as cholera and typhoid fever declined greatly during the 20th century following the advent of municipal drinking water disinfection and filtration and concurrent improvements in wastewater treatment (Cutler & Miller 2005). However, deaths from waterborne disease, as documented through waterborne disease and outbreak surveillance, continue to occur. In the Centers for Disease Control and Prevention's (CDC) Waterborne Disease and Outbreak Surveillance System (WBDOSS), waterborne transmission (for both individual cases of disease and outbreaks) includes ingestion, inhalation, or contact, and the type of water can include drinking water, recreational water, or environmental water (a broad term used to describe a variety of other exposures including consuming water directly from backcountry or wilderness streams, or inhaling aerosols from cooling towers and ornamental fountains) (Beer *et al.* 2015b). The scope of pathogens associated with waterborne disease and outbreaks is broad. In recent years, deaths have been reported as part of outbreaks caused by *Legionella* (Legionnaires' disease), hepatitis A, *Salmonella* serotype Typhimurium, and *Vibrio* spp. (Beer *et al.* 2015a, 2015b; CDC 2015b; Hlavsa *et al.* 2015). Fatal cases of other waterborne infections have also been documented by WBDOSS, including individual cases of *Naegleria fowleri* infection,

doi: 10.2166/wh.2017.301

healthcare-associated outbreaks of nontuberculous mycobacteria (NTM), or *Pseudomonas* infections associated with water (Williams *et al.* 2013; Capewell *et al.* 2015; CDC 2016).

Waterborne disease outbreaks and individual, sporadic cases (i.e., those that are not outbreak associated) of waterborne disease are reported by states to CDC through a variety of active or passive surveillance systems, such as WBDOSS (outbreaks), the Foodborne Diseases Active Surveillance Network (FoodNet) (sporadic and outbreak-associated cases), and the National Notifiable Diseases Surveillance System (NNDSS) (sporadic and outbreak-associated cases) (Table 1) (Yoder *et al.* 2010; CDC 2011, 2012, 2014; Adams *et al.* 2014; Crim *et al.* 2015). While outbreak and case surveillance reporting can reflect high-level trends in the epidemiology of waterborne disease in the United States, surveillance data do not adequately capture all illnesses or deaths from the large scope of waterborne diseases. Waterborne disease and outbreaks are investigated by local and state public health officials and voluntarily reported to the CDC. Prioritization and resources for waterborne disease and outbreak surveillance activities vary by state and by pathogen, thus these data are subject to under-reporting and can be inconsistent across jurisdictions. Additionally, these surveillance systems provide limited information on deaths, the information gathered on the case-patients can differ by pathogen, and national case surveillance systems do not exist for all waterborne pathogens of interest.

Administrative data are an alternative to surveillance data that can be used to summarize the national numbers of deaths for diseases, even those that occur rarely or are not captured in outbreak or case surveillance systems (Jhung & Banerjee 2009; Pine *et al.* 2012). To our knowledge, national numbers of deaths from pathogens that can be transmitted by water have not been previously summarized; additionally, there has been no comparison of national mortality from infectious waterborne pathogens spread by classical fecal–oral routes to environmental pathogens, such as *Legionella* and NTM, that are transmitted by other routes, including contact with and inhalation of aerosols. To better understand the recent epidemiology of waterborne disease in the United States, we used

Table 1 | Select infections, transmission information, disease surveillance system coverage, and ICD-9-CM and ICD-10 codes included in analyses

Infection	Transmission information	Individual disease/case surveillance system coverage[a]	ICD-9-CM codes[b]	ICD-10 codes[c]
Transmission by fecal–oral route				
Campylobacter	Ingestion of contaminated food or water, person-to-person, or animal-to-person	Active surveillance in 10 geographic areas through the Foodborne Diseases Active Surveillance Network (FoodNet)	008.43	A04.5
Cryptosporidium	Ingestion of contaminated food or water, person-to-person, or animal-to-person	Active surveillance in 10 geographic areas through FoodNet	007.4	A07.2
E. coli	Ingestion of contaminated food or water, person-to-person, or animal-to-person	Active surveillance in 10 geographic areas through FoodNet for Shiga toxin-producing *E. coli* (STEC) O157 and non-O157 only	008.00–008.09	A04.0–A04.4
Giardia	Ingestion of contaminated food or water, person-to-person, or animal-to-person	Passive surveillance through the NNDS (national case surveillance)	007.1	A07.1
Hepatitis A	Ingestion of contaminated food or water or person-to-person	Passive surveillance through NNDSS	070.0, 070.1	B15.0, B15.9

(*continued*)

Table 1 | continued

Infection	Transmission information	Individual disease/case surveillance system coverage[a]	ICD-9-CM codes[b]	ICD-10 codes[c]
Salmonella, non-typhoidal	Ingestion of contaminated food or water, person-to-person, or animal-to-person	Active surveillance in 10 geographic areas through FoodNet	003.0–003.9	A02.0–A02.2, A02.8–A02.9
Shigella	Ingestion of contaminated food or water or person-to-person	Active surveillance in 10 geographic areas through FoodNet	004.0–004.9	A03.0–A03.3, A03.8–A03.9
Transmission by other routes[d]				
Free-living amebae	*Naegleria fowleri*, intranasal contact with water containing ameba. *Acanthamoeba spp*., contact with water containing ameba	Passive surveillance through Free-living Ameba Surveillance System	136.2[e]	B60.1, B60.2
Legionella (Legionnaires' disease)	Inhalation of aerosolized contaminated water	Passive surveillance through NNDSS, Supplemental Legionnaires' Disease Surveillance System	482.84	A48.1
Nontuberculous mycobacteria (NTM)	Inhalation of or contact with aerosolized contaminated water; also inhalation of or contact with contaminated soil	No disease-specific surveillance	031.0–031.9	A31.0–A31.3, A31.8–A31.9
Mycobacterium avium complex (MAC)[f]			031.2	
Pulmonary NTM infection			031.0	A31.0
Otitis externa[g,h]	Contact with water contaminated by a variety of pathogens, including *Pseudomonas*	No disease-specific surveillance	380.10, 380.12, 380.14	H60.1, H60.2, H60.3, H60.8, H60.9
Pseudomonas	Inhalation, contact, aspiration, ventilator or other medical device contamination. Fatal cases usually from pneumonia or septicemia. Ubiquitous in environment	No disease-specific surveillance	041.7, 482.1, 038.43	J15.1
Pneumonia			482.1	J15.1
Septicemia[f]			038.43	
Vibrio[d,g]	Ingestion of seafood or contact with marine water	Passive surveillance through Cholera and Other Vibrio Surveillance	001.0–001.9, 005.4, 005.81	A00.0, A00.1, A05.3

[a]Does not include information on waterborne disease outbreaks (multiple cases linked to a common water exposure), which can be reported to the CDC WBDOSS.
[b]International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes are used to code clinical diagnoses in the NIS.
[c]International Classification of Diseases, 10th Revision (ICD-10) codes are used to code causes of death in the NVSS (US death certificates).
[d]Some *Vibrio* infections are transmitted by fecal–oral route, but most US deaths are associated with species acquired through ingestion of undercooked seafood contaminated with environmental *Vibrio* or contact with marine water.
[e]Effective October 1, 2008, ICD-9-CM code 136.2 was re-coded to 136.21 and 136.29.
[f]Not listed as a valid cause of death in the ICD-10 coding system.
[g]Approximate ICD-9-CM and ICD-10 coding match.
[h]Excludes people with concurrent cases of otitis media (ICD-9-CM 381.0–382.9, ICD-10 H65.0–H67.9).

administrative data to determine which pathogens that can be transmitted by water were most associated with mortality on a national scale, to describe the characteristics of persons that died, and to tabulate the numbers of annual deaths (transmitted through all routes) documented nationally from these pathogens.

METHODS

Selection of infections

For this analysis, 13 pathogens or syndromes frequently implicated in waterborne disease and outbreak surveillance, reports, or case studies in the United States were selected for inclusion (Table 1). This included infections from pathogens that can be transmitted by any type of water and any exposure route (e.g., consumption of drinking water; or inhalation of aerosolized water from a cooling tower, fountain, or sink; direct contact with recreational water). Most of the pathogens are also transmitted in other ways in addition to water exposures. The 13 infections include seven with fecal–oral transmission and six transmitted via other routes (Table 1). The goal was to investigate mortality using a subset of infections with the best available data, thus this is not an exhaustive list of infections from pathogens that can be transmitted by water. Additionally, all deaths for each infection were included. No attempt was made to separate deaths from waterborne transmission of these pathogens from deaths due to transmission via other routes.

Data sources

We analyzed data for 2003–2009 from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS), the National Center for Health Statistics' National Vital Statistics System (NVSS) death certificate records (Murphy *et al.* 2013), and selected disease surveillance systems (Yoder *et al.* 2010; CDC 2012, 2016) (Table 2).

The NIS provides de-identified, record-level data on hospitalizations, in-hospital deaths, and selected patient demographic characteristics. It is the largest all-payer database of US inpatient stays, and can be weighted to provide an estimate of all visits from US community hospitals. The NIS uses International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) to code clinical diagnoses. For the years 2003–2008, NIS included up to 15 diagnoses for each hospital stay; for 2009, NIS listed up to 25 diagnoses. We evaluated two outcome categories based on the NIS data: the *principal diagnosis*, i.e., the diagnosis deemed chiefly responsible for hospital admittance, and *all-listed diagnosis*, i.e., all diagnoses on the administrative record during the hospital stay.

NVSS death certificate data (Multiple Cause of Death files) include information on all deaths recorded in the United States, including place of death (e.g., home or hospital), age of individual at death, and up to 20 conditions that contributed to the death, coded using 4-digit International Classification of Diseases, 10th Revision (ICD-10) codes (CDC 2015a). We evaluated two outcomes derived from

Table 2 | Average annual number of deaths[a], NVSS, 2003–2009

Infection	Number with underlying cause	Number with any cause
Transmission by fecal–oral route		
Campylobacter	1	2
Cryptosporidium	2	9
E. coli	3	5
Giardia	1	2
Hepatitis A	41	103
Salmonella	34	53
Shigella	4	6
Transmission by other routes		
Free-living amebae	2	2
Legionnaires' disease	87	109
NTM	263	551
MAC[b]		
Pulmonary NTM	215	439
Otitis externa	4	14
Pseudomonas	285	1,019
Pneumonia	285	1,019
Septicemia[b]		
Vibrio	1	2

[a]Includes all deaths occurring in the United States regardless of location, i.e., in-hospital and out-of-hospital deaths.
[b]*Pseudomonas* septicemia and MAC were not listed as valid causes-of-death in the ICD-10 coding system.

the death certificate data: the *underlying cause* of death, defined as the single cause that initiated a series of events that led directly to death; and *any cause*, assigned when one of the infections of interest was coded as an underlying or contributing cause.

Additional data from national disease-specific case surveillance systems were used to supplement NVSS and NIS data, where they were available. Data on deaths caused by *Vibrio* spp. were obtained from Cholera and Other Vibrio Illness Surveillance (COVIS) for the years 2003–2009 (CDC 2012). Data on infections with the free-living amebae *Naegleria fowleri* and *Acanthamoeba* spp. were obtained from CDC's Free-living Ameba Surveillance System (Yoder *et al.* 2010; CDC 2016). *Balamuthia mandrillaris* deaths, while collected in this system, were not included because this organism is believed to be primarily a soil pathogen rather than a waterborne pathogen (Visvesvara *et al.* 2007).

Analysis

All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC). We calculated the average annual numbers of deaths associated with the selected waterborne infections using death certificate data. We then compared aggregate frequencies of in-hospital deaths for the selected waterborne infections identified in the two data sources over the seven-year study period. Weighted estimates of the average annual number of deaths, case fatality proportions, and patient characteristics including age and immune compromise status were obtained using the NIS all-listed diagnosis. Presence of an immune-compromising condition was identified using a standard list of ICD-9-CM codes (US AHRQ 2007).

We developed two approaches for combining NIS, NVSS, or surveillance data to summarize the annual number of deaths for the 13 infections (Figure 1). In the first analytic approach, based primarily on the NVSS death certificate data, we tabulated the average number of deaths with the infection listed anywhere in the death certificate record. For *Pseudomonas* septicemia, for which there is not a specific code in death certificate data, we multiplied the number of deaths with 'septicemia from other gram negative bacteria' (ICD-10 code A41.5) in death certificate data by the proportion of deaths with septicemia from other gram-negative bacteria (ICD-9-CM codes 038.40, 038.42–038.44, 038.49) attributed to *Pseudomonas* (ICD-9-CM code 038.43) in the hospital discharge data (all-listed diagnosis). In the second analytic approach, based primarily on the NIS hospital discharge data, the data source for in-hospital deaths was NIS, but out-of-hospital deaths came from the any cause death certificate data in NVSS. Although individuals are expected to be represented in both data sources, deaths were only counted once, either as in-hospital deaths (NIS) or as out-of-hospital deaths (NVSS). We used the all-listed diagnosis from NIS for all infections except *Pseudomonas* pneumonia, for which we used the principal diagnosis, because *Pseudomonas aeruginosa* can colonize lung tissues without causing clinically important infections (Fagon *et al.* 1996). In both approaches, CDC surveillance data (i.e., COVIS and Free-living Ameba Surveillance System) were used instead of death certificate or hospital discharge data to enumerate deaths from *Vibrio* infections and free-living ameba infections.

RESULTS

In the death certificate data, using underlying and any cause of death, the infections associated with the most annual deaths were *Pseudomonas* pneumonia, NTM, *Legionella* (Legionnaires' disease), hepatitis A, and *Salmonella*; all other infections were associated with fewer than 15 deaths per year, on average (Table 2). Including any cause of death from the multiple cause of death data identified more deaths for all infections except free-living ameba infections.

Table 3 facilitates comparison between hospital discharge data and death certificate data for enumerating in-hospital deaths using the first-listed cause only (principal diagnosis for hospital discharge data, underlying cause for death certificates) and any diagnosis or cause of death listed in the respective records. Using a single diagnosis or cause of death only, the hospital data identified more deaths than the death certificates for all infections except infection with hepatitis A and NTM. Using the all-listed diagnosis or any causes of death, hospital data identified more deaths for all infections.

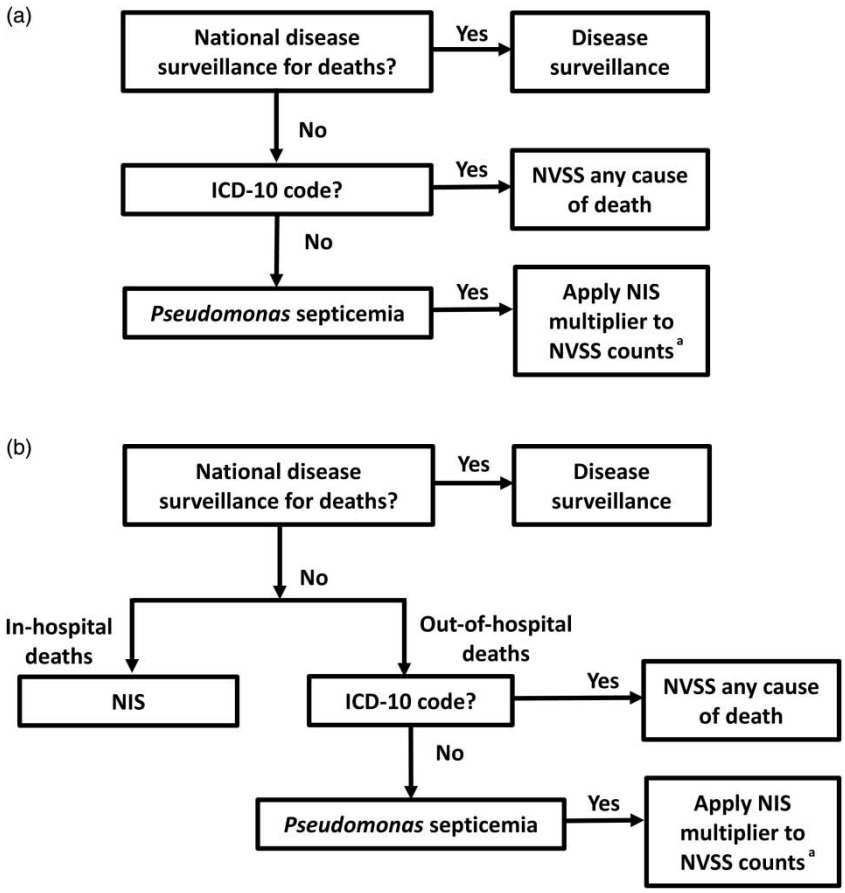

Figure 1 | Schematic showing two analytic approaches to combining national data sources to tabulate the number of deaths from 13 infections. NVSS, National Vital Statistics System; NIS, Nationwide Inpatient Sample. (a) First analytic approach, which prioritizes death certificate data. (b) Second analytic approach, which prioritizes hospital discharge data for deaths occurring in-hospital. See text for details. [a]NVSS captures number of deaths with a diagnosis of sepsis from other gram-negative bacteria. The proportion of these attributable to *Pseudomonas* specifically was estimated as the proportion of deaths due to *Pseudomonas* from all deaths involving sepsis from other gram-negative bacteria in NIS.

In the hospital discharge data, the annual number of deaths among patients ranged from 11 or fewer (i.e., below the limit of reporting for NIS data) for *Campylobacter*, *Shigella*, free-living ameba, and *Vibrio* spp., to 3,160 (95% CI 2,961–3,360) for *Pseudomonas* septicemia (Table 4). Among patients who died, median ages were lowest for *Shigella* (35 years), *Cryptosporidium* (39 years), free-living ameba (43 years), disseminated mycobacterium avium–intracellulare complex (MAC) (47 years), and *Vibrio* (54 years). For all other infections in this analysis, the median age of patients who died was 60 years and over. The highest proportions of patients with documented immune-compromising conditions were among patients who died with *Cryptosporidium* (86.2%), MAC (68.8%), *Giardia* (56.2%), and NTM (49.5%). Other conditions with more than a quarter of decedents with documented immune-compromising conditions were *Campylobacter*, *Shigella*, Legionnaires' disease, and *Pseudomonas* septicemia. As a percentage of all hospitalized cases (not shown), case fatality proportions were highest for free-living ameba infections (46.3%), *Pseudomonas* septicemia (17.3%), and Legionnaires' disease (7.9%).

Using data from disease-specific surveillance, during 2003–2009, an average of four deaths per year from infections with the free-living amebae *Naegleria fowleri* and *Acanthamoeba* spp. were reported to CDC (Table 5). During 2003–2009, an average of 42 deaths per year from *Vibrio* infection were reported to COVIS; the majority of deaths were due to *V. vulnificus*.

Table 5 lists the average annual number of deaths for each infection, as determined by the two analytic

Table 3 | Aggregate number of in-hospital deaths as enumerated by death certificates and NIS, 2003–2009

	Single code			Multiple codes		
	Death certificate underlying cause of death[a]	NIS principal diagnosis		Death certificate multiple cause of death[a]	NIS All-listed diagnosis	
Infection	No.	No.	(95% CI)	No.	No.	(95% CI)
Transmission by fecal–oral route						
Campylobacter	3	19[b]	(0–37)	6	77	(39–115)
Cryptosporidium	5	<11[b,c]		37	320	(219–422)
E. coli	20	62	(28–96)	32	241	(166–316)
Giardia	3	20[b]	(0–39)	6	167	(112–223)
Hepatitis A	183	139	(85–193)	397	1,440	(1,255–1,625)
Salmonella	190	349	(261–436)	280	672	(551–793)
Shigella	17	19[b]	(0–38)	27	48[b]	(18–77)
Transmission by other routes						
Free-living amebae	6	26[b]	(3–49)	6	36[b]	(10–63)
Legionnaires' disease	578	699	(579–819)	719	1,705	(1,481–1,928)
NTM	1,040	900	(755–1,045)	2,062	6,722	(6,028–7,416)
MAC[c]		290	(210–371)		2,885	(2,497–3,274)
Pulmonary NTM	822	569	(461–677)	1,591	3,250	(2,869–3,631)
Otitis externa	11	36[b]	(9–63)	49	641	(524–758)
Pseudomonas						
Pneumonia	1,760	10,379	(9,696–11,062)	6,190	53,312	(50,260–56,363)
Septicemia[c]		8,891	(8,294–9,489)		22,122	(20,725–23,519)
Vibrio	6	11[b]	(0–25)	7	35[b]	(9,61)

[a]Restricted to death certificates indicating that death occurred in hospital.
[b]Unstable weighted estimate.
[c]Cell counts less than 11 suppressed.
[d]*Pseudomonas* septicemia and MAC are not available as valid causes of death in the ICD-10 coding system.

approaches used to combine the data sources. Using analytic approach 1 based primarily on death certificate data, we documented that 2,444 deaths occurred annually due to the 13 infections. Of these, 180 (7%) were from the seven infections associated with fecal–oral transmission, and 2,264 (93%) were linked to the six infections with other transmission routes. Infections from three pathogens, *Legionella*, *Pseudomonas*, and NTM, were responsible for 2,204 (90%) of the deaths. Using analytic approach 2 that relied on hospital discharge data for in-hospital deaths, we documented 6,939 annual deaths from the 13 infections. Of these, 493 (7%) were associated with fecal–oral transmission and 6,446 (93%) were associated with other routes, including 6,301 (91%) of all deaths occurring with *Legionella*, *Pseudomonas*, and NTM.

DISCUSSION

By both analytic methods used to enumerate annual deaths, most deaths were from infections that result from environmental pathogens: *Pseudomonas*, *Legionella*, and NTM (90% when relying primarily on death certificate data and 91% by incorporating hospital discharge data). The administrative data used in this analysis do not contain information on transmission route, thus deaths transmitted by water and

Table 4 | Average annual inpatient deaths among patients hospitalized with selected infections, based on weighted analyses, NIS, 2003–2009

Infection	Number of deaths	(95% CI)	Age, median [Interquartile range]	Percent immune-compromised	Case fatality proportion (%)
Transmission by fecal–oral route					
Campylobacter	11	(6–16)	63 [58, 77]	36.9[a]	0.4
Cryptosporidium	46	(31–60)	39 [33, 51]	86.2	2.7
E. coli	34	(24–45)	73 [61, 84]	6.0[a]	1.8
Giardia	24	(16–32)	65 [47, 71]	56.2	1.3
Hepatitis A	206	(179–232)	60 [51, 76]	24.2	2.4
Salmonella	96	(79–113)	68 [52, 81]	24.0	1.1
Shigella	<11[a]		35 [29, 70]	29.4[a]	0.3
Transmission by other routes					
Free-living amebae	<11[a]		43 [9, 48]	14.7[a]	46.3
Legionnaires' disease	244	(212–275)	68 [57, 79]	26.8	7.9
NTM	960	(861–1,059)	62 [43, 77]	49.5	6.0
MAC	412	(357–468)	47 [37, 69]	68.8	6.4
Pulmonary NTM	464	(410–519)	70 [55, 80]	34.7	6.2
Otitis externa	92	(75–108)	74 [62, 83]	15.4	0.6
Pseudomonas					
Pneumonia	1,483	(1,385–1,580)	74 [64, 81]	17.6	6.6
Septicemia	3,160	(2,961–3,360)	68 [57, 78]	34.9	17.3
Vibrio	<11[a]		54 [48, 65]	15.3[a]	5.3

Note: Analyses based on the all-listed diagnosis, except *Pseudomonas* pneumonia, which is based on principal diagnosis only. See text for details.
[a]Cell counts less than 11 suppressed.

by other sources were counted. However, this analysis echoes recent findings from surveillance for waterborne disease outbreaks in the United States, in which *Legionella* has emerged as the leading cause of death in reported waterborne disease outbreaks associated with drinking water and environmental water sources (Beer *et al.* 2015a, 2015b).

The widespread use of water for industrial, healthcare, cooling, decoration, and other purposes in high-income, developed settings has created ecological niches for *Legionella* spp., as well as other pathogens including *Pseudomonas* spp. and NTM. These environmental pathogens do not rely on human hosts for their life cycle, and, as such, do not have a fecal source. They have emerged as important causes of non-gastrointestinal illness associated with water systems in the built environment because they commonly grow in biofilms and multiply in plumbing systems and other built environment water systems such as cooling towers (Cangelosi *et al.* 2005; Falkinham *et al.* 2015). However, few literature estimates exist for the proportion of transmission due to water for these three pathogens.

US Environmental Protection Agency (EPA) regulations that have reduced drinking water-associated outbreaks of gastroenteritis do not apply to the plumbing pipes within homes or other buildings (US EPA 2012). Within buildings, plumbing systems have more stagnant water, a lower disinfectant residual (i.e., lower or non-detectable levels of chlorine or other disinfectant), and often warmer temperatures, all of which contribute to biofilm development and growth (Thomas & Ashbolt 2011; Williams *et al.* 2013). Biofilms have a complex ecology, and can occur in various settings and throughout water systems (Thomas & Ashbolt 2011; Chowdhury 2012; Lu *et al.* 2015). Biofilm-associated pathogens can reach a susceptible host when they are sloughed or disrupted from these biofilms and released into piped water. Furthermore, biofilm-associated pathogens

Table 5 | Average annual deaths from infections enumerated using two analytic approaches, United States, 2003–2009

	Analytic approach 1[a]		Analytic approach 2[b]	
Infection	**Data source**	**Number of deaths**	**Data source**	**Number of deaths**
Transmission by fecal–oral route				
Campylobacter	NVSS[c]	2	NIS, NVSS[d]	12
Cryptosporidium	NVSS[c]	9	NIS, NVSS[d]	50
E. coli	NVSS[c]	5	NIS, NVSS[d]	35
Giardia	NVSS[c]	2	NIS, NVSS[d]	25
Hepatitis A	NVSS[c]	103	NIS, NVSS[d]	253
Salmonella	NVSS[c]	53	NIS, NVSS[d]	109
Shigella	NVSS[c]	6	NIS, NVSS[d]	9
Total, fecal–oral route		**180**		**493**
Transmission by other routes				
Free-living amebae	Free-living Ameba Surveillance System	4	Free-living Ameba Surveillance System	4
Legionnaires' disease	NVSS[c]	109	NIS, NVSS[d]	250
NTM	NVSS[c]	551	NIS, NVSS[d]	1,216
Otitis externa	NVSS[c]	14	NIS, NVSS[d]	99
Pseudomonas				
Pneumonia	NVSS[c]	1,019	NIS, NVSS[e]	1,618
Septicemia	NVSS, NIS[f]	525	NIS, NVSS[g]	3,217
Vibrio	COVIS	42	COVIS	42
Total, other routes		**2,264**		**6,446**
Total, all transmission modes		**2,444**		**6,939**

NVSS, National Vital Statistics System; NIS, Nationwide Inpatient Sample; COVIS, Cholera and Other Vibrio Surveillance.

[a]In analytic approach 1, for most pathogens, the average number of deaths with the pathogen or syndrome listed anywhere on the death certificate was used as the primary data source; see Methods section text for details.

[b]In analytic approach 2, for most pathogens, we used data from the NIS for in-hospital deaths, but used the death certificates to capture out-of-hospital deaths; see Methods section text for details.

[c]Listed in any position as a cause of death on death certificate.

[d]Uses NIS any diagnosis for in-hospital deaths and NVSS any cause data for out-of-hospital deaths.

[e]Uses NIS principal diagnosis for in-hospital deaths and NVSS any cause data for out-of-hospital deaths.

[f]Two data sources were combined to estimate total. NVSS captures number of deaths with a diagnosis of sepsis from other gram-negative bacteria. The proportion of these attributable to *Pseudomonas* specifically was estimated as the proportion of deaths due to *Pseudomonas* from all deaths involving sepsis from other gram-negative bacteria in NIS (15.4%).

[g]Uses NIS principal diagnosis for in-hospital deaths, and 15.4% of out-of-hospital deaths for septicemia with other gram-negative bacteria from NVSS.

can grow in recreational and other environmental water sources such as poorly maintained hot tubs, cooling towers, and decorative fountains, and can give rise to cases of illness in a variety of settings when aerosols are produced (Beer *et al.* 2015b; Hlavsa *et al.* 2015). The emerging exposures to biofilms present in plumbing systems, cooling towers, fountains, and hot tubs may have contributed to the predominance of environmental pathogens as causes of death.

Environmental pathogens differ from most fecal–oral pathogens in that they result in longer hospitalizations and more severe outcomes for persons who are older or have immune-compromising conditions, (i.e., they are, to some extent, opportunistic pathogens) (Collier *et al.* 2012; Falkinham *et al.* 2015). The previously documented association of these infections with older age was borne out of our analysis of hospital discharge data; however, the proportion documented as immune-compromised was not

consistently higher in these pathogens than the others in our analysis. For example, in our analysis, *Giardia*, which is not typically considered opportunistic, was associated with higher proportions of decedents having documented immune-compromising conditions when compared to decedents with Legionnaires' disease, which is considered opportunistic.

Our findings suggest that mortality from the selected pathogens in the United States is not primarily attributable to fecal–oral pathogens. This observation may reflect, in part, access to healthcare and treatments that make it relatively unlikely that gastroenteritis results in death (CDC 1999). In addition, low mortality from gastrointestinal infections may stem from successes of drinking water treatment regulations from the US EPA, which have reduced microbial contamination and, in consequence, waterborne disease transmission of gastrointestinal diseases resulting from the ingestion of fecally contaminated water (Craun *et al.* 2010; Beer *et al.* 2015a; CDC 2015b). EPA regulations do not apply to individuals served by private wells and other individual water systems, and a large number of waterborne disease outbreaks associated with drinking water occur in these systems; however, these serve a minority of households in the United States (Craun *et al.* 2010). Chlorine-sensitive gastrointestinal pathogens resulted in only eight drinking water-associated outbreaks during the 2011–2012 outbreak reporting cycle, although these accounted for over half of the total outbreak-cases (Beer *et al.* 2015a), demonstrating that these pathogens still have potential to drive high-impact waterborne disease outbreaks when failures in improved water treatment and management occur. *Cryptosporidium,* a highly chlorine-tolerant parasite, arose as an important cause of diarrhea and severe illness or death in the immuno-compromised during the 1980s and 1990s. *Cryptosporidium* infections have become especially linked with swimming in chlorinated pools, an activity that gained popularity with increased leisure time. Since 1988, when the first reported cryptosporidiosis outbreak from treated recreational water occurred, the annual number of these outbreaks has increased significantly, although recreational water-associated outbreaks rarely have fatal cases. In 2011–2012, 90 recreational water-associated outbreaks from 32 states and Puerto Rico were linked to 1,800 cases of illness and one death (Hlavsa *et al.* 2015).

This analysis did not directly document deaths due to waterborne transmission. All deaths for infections of each pathogen were included, and no attempt was made to separate deaths from waterborne transmission from deaths due to transmission via other routes. In part, this is because few or no estimates of the proportion of transmission attributable to water exist for several pathogens of interest, including *Pseudomonas* spp. and NTMs. However, for some infections studied, the attributable waterborne fraction is likely to be high (e.g., *Legionella*, *Naegleria*), while for others it is probably much lower (e.g., non-Typhoidal *Salmonella*, hepatitis A). Published attribution estimates for several of the fecal–oral pathogens included in our study show that the proportion of waterborne transmission varies by pathogen as follows: 1–6% for Hepatitis A virus (0–27% CI range) (Vally *et al.* 2014; Butler *et al.* 2015; WHO 2015), 2–8% for *Salmonella* (0–35% CI range) (Vally *et al.* 2014; Butler *et al.* 2015; WHO 2015), 6–11% for *Campylobacter* (0–32% CI range) (Vally *et al.* 2014; Butler *et al.* 2015; WHO 2015), 37% for *Cryptosporidium* (8–72% CI range) (Butler *et al.* 2015; WHO 2015), and 42–48% for *Giardia* (5–75% CI range) (Butler *et al.* 2015; WHO 2015). Thus, it is important to consider that the deaths reported here represent the documented totals for the pathogens and syndromes, and therefore include resulting infections from all possible modes of transmission. Additionally, the datasets used in this analysis are expected to underestimate the number of deaths attributed to specific pathogens. Thus, the numbers of deaths we document here are likely to be conservative estimates of total deaths due to underdiagnosis, limitations to the sensitivity of death certificates and hospital discharge data for identifying deaths from infections (Barber *et al.* 2013; Govindan *et al.* 2014), and limited information on deaths that occur outside of a hospital setting. Not surprisingly, our analytic approach based on hospital discharge data identified nearly three times as many deaths as the approach based on death certificates. Individuals often die having serious chronic health conditions in addition to infections; death certificates tend to give more weight to the chronic conditions, and less to infections that lead to death more proximally (Govindan *et al.* 2014). Furthermore, for patients who die out of hospital, and those who die in hospital with both infections and terminal chronic diseases, the precise etiology of infections might not

be investigated thoroughly. Although hospital discharge data also have low sensitivity for identifying infections and do not supply information on deaths occurring outside of the hospital, they may be a better source of pathogen-specific data than death certificates. A review of studies on the validity of administrative data to identify cases of severe sepsis concluded that ICD-9 codes for these conditions have high specificity (median of five studies, 98.5%) and lower sensitivity (median of seven studies, 42.4%) (Jolley *et al.* 2015). A Swedish registry-based study found that sensitivity was limited for identifying primary pneumonia in administrative data (38.2%) but specificity was high (98.6%) (Gedeborg *et al.* 2007). Finally, a study of administrative data from the United States Department of Veterans Affairs calculated a 70% positive predictive value of both pneumonia (not specific to pathogen) and NTM infection codes (Schneeweiss *et al.* 2007).

In spite of limitations to the sensitivity and specificity of hospital discharge data and death certificate data already noted, the stability and availability of these data makes them useful for monitoring disease outcomes across a wide range of conditions. Outbreak surveillance is suitable for documenting disease transmission through water; however, it is not a reliable source of information on deaths from pathogens with potential for waterborne transmission. For the United States, the combination of administrative data and death certificate data used here may be the best means of obtaining systematic data on deaths from pathogens that can be transmitted by water; importantly, these methods can be repeated annually as new data are made available, allowing for the tracking of waterborne disease-associated mortality over time. These data allow for a look at waterborne diseases beyond the enteric illnesses transmitted through drinking water and provide insight into the epidemiology of pathogens that can be transmitted by water.

CONCLUSIONS

In summary, we documented that infections from the 13 selected pathogens and syndromes were associated with nearly 7,000 deaths each year in the United States. Environmental and biofilm-associated pathogens, to which individuals are exposed through inhalation, contact, and other routes, are associated with over 90% of the documented deaths. Current regulations for drinking water systems and recreational water venues have largely had a goal of limiting the transmission of pathogens by the fecal–oral route; efforts to reduce illness and death from environmental pathogens will require a variety of behavioral and engineering strategies depending on their environmental niches and human interactions with water. For example, engineering standards have been developed to control *Legionella* growth in building water systems (ASHRAE 2015), and limiting the amount of water entering the nose while swimming in warm freshwater venues could reduce the risk of acquiring *Naegleria* infections (Yoder *et al.* 2010). The prominence of environmentally associated pathogens suggests that biofilms, commonly found in water, could be an important focal point for prevention efforts. Additionally, work is needed to better understand attributable proportions of waterborne transmission for these infections, so that targeted prevention efforts can reduce the mortality associated with these infections in the United States.

DISCLAIMER

The findings and conclusions in this article are those of the authors, and do not necessarily represent the official position of the US CDC.

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First received 8 December 2016; accepted in revised form 3 February 2017. Available online 20 March 2017