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Prevalence of and Risk Factors for Hepatitis C Virus Infection in World Trade Center Responders

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Abstract

Background: *The risk of hepatitis C virus (HCV) infection among emergency responders exposed to human remains, blood/bodily fluids, and/or sewage is unknown.* **Methods:** *A cross-sectional study of 3,871 World Trade Center General Responder Cohort (WTCGRC) members followed at the Icahn School of Medicine at Mount Sinai, born from 1945-1965, and recruited from 2016-2018 were tested for HCV infection, and prevalence was compared to National Health and Nutrition Examination Survey data from 2003 to 2012. A nested case-control study compared 61 HCV antibody positive cases to 2571 controls. Multivariable logistic regression models adjusting for time of birth, traditional HCV risk factors, and type of work at the World Trade Center (WTC) site, determined if contact with human remains, blood/bodily fluids, and/or sewage at the WTC site was associated with HCV infection.* **Results:** *The age-standardized point prevalence of HCV infection among WTCGRC members was 2.98% [95% CI (2.39, 3.56)] and in the US population was 3.33% [95% CI (2.54, 4.11)] [% difference=0.35%, 95% CI (- 0.31%, 1.01%), P=0.47]. In separate multivariable models, adjusting for possible confounders, contact with human remains was not associated with HCV infection [OR=1.10, 95% CI (0.63, 1.91), P=0.74)], contact with blood and/or bodily fluids was not associated with HCV infection [OR=1.45, 95% CI (0.82, 2.56), P=0.20], and contact with sewage was associated with HCV infection [OR=1.72, 95% CI (1.00, 2.98), P=0.05].* **Conclusion:** *Contact with sewage may increase the risk of HCV infection.*

1. Introduction

Chronic hepatitis C virus (HCV) infection increases the risk of liver cirrhosis and hepatocellular carcinoma [1, 2]. While multiple risk factors for HCV infection have been recognized, at least 20% of persons with HCV infection do not have a known risk factor [3, 4] which suggests there are unrecognized risk factors. The Occupational Safety and Health Administration of the US Department Labor standards for blood-borne pathogens (29 Code of Federal Regulations 1910.1030) [5] and personal protective equipment (29 Code of Federal Regulations 1910 Subpart 1) [6] require employers to protect workers from occupational exposure to infectious agents. Thus, persons employed in

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occupations with expected exposure to human remains, blood or bodily fluids, and stool with visible blood are educated about the risks of HCV from these agents, and provided with and expected to wear protective gear. During the course of an emergency response, workers and volunteers may be unexpectedly exposed to these agents. The prevalence of and risk factors for HCV infection has not been previously assessed in persons exposed to these agents during an emergency response.

The World Trade Center General Responders Cohort (WTCGRC) comprises workers and volunteers who participated in the emergency response activities at the World Trade Center (WTC) site and are followed at the Icahn School of Medicine at Mount Sinai and other medical institutions to monitor their health. At their enrollment interview, WTCGRC members were specifically asked about contact with "human remains", "blood or bodily fluids", and "sewage" during their WTC activities. This cohort offers an opportunity to study the risk of HCV infection in emergency response workers exposed to these agents.

A cross-sectional study determined the prevalence of HCV in WTC responders and compared it to the prevalence of HCV in the US population. A nested case-control study then determined if contact with human remains, blood or bodily fluids, and sewage (wastewater and excrement conveyed in sewers) during emergency response work is associated with an increased risk of HCV infection.

2. Methods

The WTCGRC has been described elsewhere [7]. The cohort consists of WTC responders who worked or volunteered in lower Manhattan, or the Staten Island landfill or barge-loading piers for 4 hours or more from September 11 to 14, 2001; 24 hours or more during September 2001; or 80 hours or more from September 2001 to December 2001. Recruitment began on July 16, 2002, and is ongoing.

Recruitment into WTCGRC was done by extensive outreach [7]. Participation is voluntary and includes a comprehensive baseline examination which includes collection of questionnaire data, a history and physical examination, and collection of bloodwork. Monitoring assessments are given every 12 to 18 months and similarly include collection of questionnaire data, a history and physical examination, and collection of bloodwork. All assessments occur at one of several World Trade Center Clinical Centers of Excellence [8]. As of March 31, 2014, 33,863 persons were eligible for inclusion in the cohort and had completed a Visit 1 [9]. WTCGRC participants may participate in health monitoring yet opt out of research. Thus, there are members of the WTCGRC who routinely attend their monitoring visits, but their data is unavailable to researchers.

According to CDC, persons born from 1945-1965 are at higher risk for HCV infection than other birth cohorts [10]. For this HCV Study, responders who presented to the Icahn School of Medicine at Mount Sinai site for a WTCGRC visit (Visit 1 or higher), and were born from 1945 through 1965, were given information about HCV infection and offered study participation that included free HCV testing.

Interested persons completed the informed consent process, signed the informed consent document, and completed the HCV Risk Factor Questionnaire (see below). Recruitment began on December 15, 2016, with materials in English. Spanish materials were available on November 3, 2017, and Polish materials were available on May 4, 2018. The last day of recruitment was July 12, 2018. Persons who declined to participate in the WTCGRC Research Study were included in this study at their discretion, and with the understanding that data beyond the HCV Risk Factor Questionnaire would not be accessed. Enrollment continued until the study sample size was reached. (Sample size is defined below.)

The HCV Risk Factor Questionnaire assessed demographic data (year of birth, country of origin, current type of medical insurance); previous testing, results, and treatment for HCV infection; and traditional risk factors for HCV infection (blood transfusion or organ transplant before July 1992, receipt of clotting factor concentrate produced before 1987, receipt of long-term hemodialysis, receipt of blood from an HCV-infected donor, birth to an HCV-infected mother, history of human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), history of injecting drug use (IDU), and needle stick, sharps, or mucosal exposure to HCV-infected blood as a health care, emergency medical, or public safety worker) [10]. As a point of clarification, the HCV Risk Factor Questionnaire was administered on the date of HCV antibody testing and asked participants if they ever had any of the traditional risk factors for HCV infection (Supplementary Material, Table S1).

After completing the HCV Risk Factor Questionnaire, study participants completed their usual visit. In addition to blood drawn for routine testing, two 2 mL tubes of blood were drawn. Blood from the first tube was tested for HCV antibody. For those with a positive HCV antibody test, blood from the second tube was tested for HCV RNA using polymerase chain reaction (PCR). Otherwise, blood from the second tube was discarded. Persons with a positive HCV antibody test were defined as having current or prior HCV infection. Current HCV infection was defined by detectable HCV ribonucleic acid (RNA) and prior HCV infection was defined by undetectable HCV RNA. All participants were notified of their results by letter, telephone call, or email based on their preference. Persons with current HCV infection received telephone calls with offers of referral to liver specialists at either the co-located Mount Sinai Liver Medicine Practice or a federally qualified health center in their preferred location. Persons who attended at least one outpatient visit with a liver specialist were defined as being linked to care.

2.1. Statistical Analysis

2.1.1. Cross-sectional Study

For the cross-sectional study, the age-standardized prevalence of HCV infection in this study sample was determined using the US population in the 2010 census as the standard population, and was compared to the age-standardized prevalence of anti-HCV antibodies in the general US population based on National Health and Nutrition Examination Survey (NHANES) data from 2003 through 2012 using the appropriate weights [11]. The sample size was calculated to provide adequate statistical power for this analysis. With 3900 persons and an expected prevalence of HCV in the US population of 3.2%, this analysis would have 80% power to detect as statistically significant (at $\alpha=0.05$) a 0.8% difference between the expected prevalence of HCV infection in the US population (3.2%) and the prevalence of HCV among members of the WTCGRC (either$\geq$4.0% or$\leq$2.4%).

2.1.2. Nested Case-control Study

2.1.2.1. Study Population

WTCGRC members who consented to research were eligible for inclusion in the nested case-control study. A case was defined as a person with current or prior HCV infection and was measured by a positive HCV antibody test. Controls were persons without HCV infection. Persons with an indeterminate HCV antibody test were removed from the analysis. (All data used in the nested case-control study and the data source are provided in Supplementary Material, Table S1.)

2.1.2.2. Three Main Exposures

Data for the three main exposures were obtained from the WTCGRC baseline questionnaire. Within the baseline questionnaire, study personnel determined if WTCGRC members had participated in WTC activities in three intervals: September through October 2001, November through December 2001, and January through June 2002. For those intervals in which the member participated, study personnel asked if they had “contact” with “human remains”, “blood or bodily fluids”, and/or “sewage”. Participants were defined as having exposure if they reported contact during any of these three periods.

2.1.2.3. Possible Confounders

Possible confounders for this study included traditional HCV risk factors, demographic characteristics, and activities at the WTC site. Traditional HCV risk factors were obtained from the HCV Risk Factor Questionnaire. Sex, race, and ethnicity were obtained from the WTCGRC baseline questionnaire. Year of birth, country of birth, and insurance status were obtained from the Hepatitis C Risk Factor Questionnaire. While household contacts with HCV infection [12], sexual risk behaviors [13], and level of education [14] have been identified as risk factors for HCV infection, these characteristics were not captured in our questionnaire and were therefore not included in this analysis.

Data on activities at the WTC site was obtained from the WTCGRC baseline questionnaire and included year of enrollment in the WTCGRC, type of work done as a volunteer or worker, use of gloves, use of personal protective equipment, and seeking care for injuries which pierced the skin. For type of work done as volunteer or worker, participants were handed a list of types of work organized by Department of Labor Codes and WTC Activity codes and asked "What activity code best describes what you were doing during this period?" for each of four periods (September 2001, October 2001, November to December 2001, and January to June 2002). Study personnel entered up to three activity codes for each period. A time-weighted measure of protective glove use and protective clothing use was based on participants' reported use of protective gloves and/or protective clothing (rarely/never, sometimes, most of the time, all the time) during each of each three time periods: September-October, November-December, and January-June.

WTCGRC participants reported up to four injuries or illnesses acquired during the WTC activities for which they sought medical care while working at the WTC site. Members were identified as having skin/mucous membrane injury if they indicated seeking medical care for an abrasion, amputation, blister, burn, contusion (bruise), crush, cut/puncture, eye injury, foreign body, and skin irritation/rash.

2.1.2.4. Analytic Approach

It was decided *a priori* that the final analysis would adjust for traditional HCV risk factors and birth year. Thus, the nested case-control study analyses were limited to participants who had complete exposure data for at least one of the three main exposures, complete data on the traditional HCV risk factors, and reported a year of birth.

Demographic characteristics and activities at the WTC site were evaluated in univariable analysis. Characteristics with a p-value of <.20 were further evaluated in forward, backward, and stepwise manual and machine-assisted multivariable logistic regression analysis with HCV infection as the outcome to find those characteristics independently associated with HCV infection (P ≤.05). Characteristics independently associated with HCV infection were identified as possible confounders and were adjusted for in further analyses.

The final analysis included three multivariable logistic models, one for each main exposure. These models included HCV infection as the outcome and were adjusted for age, traditional HCV risk factors, and the identified possible confounders.

This study was approved by the Icahn School of Medicine Institutional Review Board (Study 16-01343) which conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All participants gave informed consent before taking part. All statistical analyses were conducted in SAS (Version 9.4). A p-value ≤ 0.05 was considered statistically significant. All study data are protected with an Assurance of Confidentiality.

3. Results

3.1. Cross-sectional Study

A total of 3,935 WTCGRC members enrolled in this current study. Of those, 64 persons were excluded (18 born outside the birth cohort, 21 missing laboratory data, 15 with "indeterminate" HCV antibody results with negative HCV RNA PCR testing, and 10 withdrawals). Of the remaining 3,871, 109 (2.8%) had HCV infection.

The prevalence of HCV infection in study participants was similar to the prevalence in the US population (Supplementary Material, Figure S1). The age-standardized point prevalence of HCV infection in the WTC Cohort was 2.98% [95% CI (2.39, 3.56)] and in the US population was 3.33% [95% CI (2.54, 4.11)] [% difference=0.35%, 95% CI (-0.31%, 1.01%), P=0.47].

Of the 109 persons with antibodies to HCV, 14 (13%) had current infection based on the presence of HCV RNA in their blood, 39 (36%) reported previous treatment for HCV infection, 39 (36%) reported no previous treatment for HCV infection, and 17 (16%) reported they did not know if they had been treated or did not answer the question. Because HCV treatment status is unknown in these last 17 persons, the range of spontaneous clearance of HCV infection in this group is between 36% (39/109) and 51% (56/109).

Of the 14 persons diagnosed with current HCV infection, two were in care for HCV infection at the time of screening, and 12 were referred for specialized care by study personnel. Of the 12, 11 (92%) requested a referral to the Mount Sinai Liver Medicine Practice, and one requested a referral to a federally qualified health center based on insurance status. Of the 12 referred for care, 10 (83%) were linked to care (attended an in-person appointment with a liver specialist). Of the 10 linked to care, nine persons were prescribed and received anti-HCV therapy and achieved sustained virologic response.

3.2. Nested Case-control Study

Of the 3,871 participants in the cross-sectional study, 507 persons did not have available exposure data (89 did not consent to participate in the WTCGRC Research Study, eight had data that were not yet integrated into the WTCGRC Research Study database, and 410 did not have complete data on at least one of the three main exposures) leaving 3,364 persons. Of the 3,364 persons, 732 did not provide complete information on traditional HCV risk factors leaving 2,632 persons for the nested case-control study (Table 1).

Of the 2,632 persons included in the nested case-control study, 61 (2.3%) had HCV antibodies indicating prior or current HCV infection and were identified as cases.

Table 1. Participants with and without hepatitis C virus (HCV) antibodies in the nested case-controls study[a].

Characteristics		HCV Antibody+ N=61 (%)	HCV Antibody- N=2571 (%)	P-value
Demographics				
Sex				.34[b]
	Male	54 (89)	2160 (84)	
	Female	7 (11)	411 (16)	
Time period of birth				.001[b]
	1945 - 1949	3 (5)	210 (8)	
	1950 - 1954	20 (33)	391 (15)	
	1955 - 1959	18 (30)	694 (27)	
	1960 - 1965	20 (33)	1276 (50)	
Race				.33[b]
	White	30 (49)	1433 (56)	
	Multi-Racial	14 (23)	411 (16)	
	Black	11 (18)	451 (18)	
	Asian	0	37 (1)	
	American Indian / Alaskan Native	1 (2)	7 (0.3)	
	Pacific Islander	0	1 (0.1)	
	Not answered	5 (8)	231 (9)	
Latino (N=2533)				.35[b]
	Yes	16 (28)	554 (22)	
	No	42 (72)	1921 (78)	

Table 1 (*Continued*)

Characteristics		HCV Antibody+ N=61 (%)	HCV Antibody- N=2571 (%)	P-value
Insurance status (N=2501)				.005[b]
	Medicaid	3 (5)	75 (3)	
	Medicare	17 (31)	369 (15)	
	No insurance	2 (4)	60 (2)	
	Private insurance	33 (60)	1942 (79)	
Born in the United States (N=2566)				.11[b]
	Yes	51 (86)	1950 (78)	
	No	8 (14)	557 (22)	
Main Exposures				
Contact with human remains				.95[b]
	Yes	28 (46)	1190 (46)	
	No	33 (54)	1381 (54)	
Contact with blood and/or bodily fluids				.25[b]
	Yes	22 (36)	752 (29)	
	No	39 (64)	1819 (71)	
Contact with Sewage				.02[b]
	Yes	37 (61)	1175 (46)	
	No	24 (39)	1396 (54)	
Traditional HCV risk factors				
	Blood transfusion or organ transplant before July 1992	1 (2)	36 (1)	.58[c]
	Receipt of clotting factor concentrate produced before 1987	0	5 (0.2)	1.00[c]
	Receipt of long-term hemodialysis	1 (2)	2 (0.1)	.07[c]
	Receipt of blood from an HCV-infected donor	1 (2)	8 (0.3)	.19[c]
	Born to HCV-infected mother	0	12 (0.5)	1.00[c]
	HIV or AIDS	1 (2)	2 (0.1)	.07[c]
	History of injecting drug use	3 (5)	0	<.001[c]
	Needle stick, sharps, or mucosal exposure to HCV-infected blood as a health care, emergency medical or public safety worker	1 (2)	34 (1)	.56[c]
Activities at the WTC site[d]				
	Year of enrollment in the World Trade Center General Responder Cohort			.85[b]
	2002-2005	31 (51)	1219 (47)	
	2006-2009	17 (28)	764 (30)	
	2010-2013	4 (7)	241 (9)	
	2014-2018	9 (15)	347 (14)	
Type of work at WTC site (N=2611)‡				
	Laborers	3 (5)	31 (1)	.004[c]
	Perimeter Security	2 (3)	543 (20)	<.001[c]

Table 1 (*Continued*)

Characteristics		HCV Antibody+ N=61 (%)	HCV Antibody- N=2571 (%)	P-value
	Police Officer	0	344 (13)	<.001[c]
	Truck drivers	3 (5)	21 (1)	.02[c]
Time-weighted glove use (N=2562)				.02[e]
	Rarely/Never	12 (20)	741 (30)	
	Sometimes	6 (10)	442 (18)	
	Most of the time	16 (27)	505 (20)	
	Always	26 (43)	814 (33)	
Time-weighted personal protective equipment use (N=2562)				.54[e]
	Rarely/Never	43 (73)	1840 (74)	
	Sometimes	9 (15)	216 (9)	
	Most of the time	2 (3)	118 (5)	
	Always	5 (8)	304 (12)	
Received medical care for an injury which pierced the skin (N=1720)				.76[c]
	Yes	2 (5)	137 (8)	
	No	35 (95)	1546 (92)	

HCV: hepatitis C virus, WTC: World Trade Center, HIV: human immunodeficiency virus, AIDS: acquired immunodeficiency syndrome
[a] Unless otherwise noted, data is presented for all 61 cases (persons who had HCV antibodies) and 2571 controls (persons without HCV antibodies).
[b] Analyzed using Chi-square analysis.
[c] Analyzed using Fisher's Exact analysis.
[d] Data on all categories of work at the WTC site are included in Supplementary Material, Table S2.
[e] Analyzed using Chi-square test for linear trend.

Participants in the nested case-control study were 84% men, 56% white, 18% black, 16% multi-racial, 9% not-reported, 1% Asian, 0.3% American Indian and Alaskan Native, 0.04% Pacific Islander, and 23% Latino. There was a higher prevalence of black WTCGRC members in this HCV Study compared to the full WTCGRC Research Study [7]. The median age on enrollment was 58 years [interquartile range (IQR) 54, 62].

Cases and controls were of similar sex, race, ethnicity, insurance status, and USA birth but differed in time period of birth (P=.001) (Table 1). Cases and controls did not differ in their contact with human remains (P=.95) and blood and/or bodily fluid (P=.25), but did differ in their contact with sewage (P=.02).

After evaluating demographic characteristics and activities at the WTC site in univariable and multivariable analysis adjusting for time period of birth and traditional HCV risk factors, working or volunteering for perimeter security at the WTC site, and working or volunteering as a truck driver at the WTC site were both associated with HCV infection. (Characteristics of the persons working or volunteering for perimeter security and characteristics of persons working or volunteering as a truck driver at the WTC are presented in Supplementary Materials, Table S3, and Table S4, respectively.) Thus, the final models adjusted for time period of birth, traditional HCV risk factors, working or volunteering for perimeter security at the WTC site, and working or volunteering as a truck driver at the WTC site.

In multivariable logistic regression models, adjusting for possible confounders (time period of birth, traditional HCV risk factors, perimeter security work at the WTC, driving a truck during WTC), contact with human remains was not associated with HCV infection [Table 2, Model 1: OR=1.10, 95% CI (0.63, 1.91), P=0.74) and contact with blood and/or bodily fluids was not associated with HCV infection [Table 2, Model 2: OR=1.45, 95% CI (0.82, 2.56), P=0.20]. Contact with sewage was associated with HCV infection [Table 2, Model 3: OR=1.72, 95% CI (1.00, 2.98), P=0.05].

4. DISCUSSION

This study suggests the prevalence of HCV infection in WTCGRC members born from 1945 through 1965 is comparable to that of the US population, the spontaneous HCV infection clearance rate in this population is similar to the general

Table 2. Multivariable logistic regression models for risk of HCV infection (N=2632)[a].

Characteristics		HCV Antibody+ N=61 (%)	HCV Antibody- N=2571(%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Main exposures						
Contact with human remains						
	Yes	28 (46)	1190 (46)	1.10 (0.63, 1.91)[b]		
	No	33 (54)	1381 (54)	1.00		
Contact with blood and/or bodily fluids						
	Yes	22 (36)	752 (29)		1.45 (0.82, 2.56)[c]	
	No	39 (64)	1819 (71)		1.00	
Contact with sewage						
	Yes	37 (61)	1175 (46)			1.72 (1.00, 2.98)[d]
	No	24 (39)	1396 (54)			1.00
Other characteristics independently associated with HCV infection						
Perimeter security during WTC activities						
	Yes	2 (3)	518 (20)	0.17 (0.04, 0.70)[e]	0.17 (0.04, 0.70)[e]	0.17 (0.04, 0.70)[e]
	No	59 (97)	2032 (80)	1.00	1.00	1.00
Truck driver during WTC activities						
	Yes	3 (5)	21 (1)	6.26 (1.73, 22.68)[f]	6.65 (1.86, 23.74)[g]	6.27 (1.76, 22.27)[f]
	No	58 (95)	2529 (99)	1.00	1.00	1.00

HCV: hepatitis C virus, WTC: World Trade Center
[a] *All models adjusted for time period of birth (1945- 1949, 1950-1954, 1955-1959, 1960-1965) and traditional HCV risk factors (blood transfusion or organ transplant before July 1992, receipt of clotting factor concentrate produced before 1987, receipt of long-term hemodialysis, receipt of blood from HCV-infected donor, birth to HCV-infected mother, history of human immunodeficiency virus infection or acquired immunodeficiency syndrome, history of injecting drug use, and needle stick, sharps, or mucosal exposure to HCV-infected blood as a health care, emergency medical, or public safety worker).*
[b] *P = .74*
[c] *P = .20*
[d] *P = .05*
[e] *P = .01*
[f] *P = .005*
[g] *P = .004*

population, and an ongoing cohort study is an effective site for screening for HCV and linkage to care. Contact with sewage at the WTC site may be associated with an increased risk of HCV infection.

The similar prevalence of HCV infection in WTCGRC members born from 1945 through 1965 and in the general US population initially appears reassuring. However, the WTCGRC members, by definition, are persons who worked at the WTC site. Comparisons of groups of workers to the general population may suffer from the "healthy worker effect" bias. In their often-cited article, Li and Sung write, "the 'healthy worker effect' reflects that an individual must be relatively healthy to be employable in a workforce, and both morbidity and mortality rates within the workforce are usually lower than in the general population" [15]. Thus, the similar prevalence of HCV infection in WTCGRC members and the general US population may be reassuring or may reflect an increased risk of HCV infection in WTCGRC workers, which is obfuscated by the healthy worker effect. While Li and Sung would recommend comparing HCV infections among members of the WTCGRC cohort to an external work comparison group [15], such a comparison is beyond the scope of this current study.

The rate of spontaneous clearance of HCV infection in this study was between 36% and 51%, consistent with the current literature. While the oft-cited systematic review of spontaneous clearance by Micallef et al. found spontaneous clearance of HCV infection to be 26% (95% CI: 22%, 29%) [16], a more recent systemic review and meta-analysis of studies with longer follow-up done by Aisyah et al. found spontaneous clearance at 24 months to be 37.1% (95% CI: 23.7%, 52.8%) [17].

This study was effective at using an existing cohort study to screen persons for HCV infection and to link infected persons with care. Previous research has suggested that sites which both screen for HCV and provide treatment for HCV are more successful at linking HCV-infected persons to care. Galbraith et al reported 21% (21/100) of patients with HCV infection were linked to care after screening done in a hospital emergency department, a site in which screening and treatment were not co-located [18]. In contrast, Jonas et al reported 81% (214/277) linkage to care in a study of 11,200 persons born from 1945 through 1965 who were screened during routine outpatient visits at Kaiser Permanente [19], a site in which screening and treatment were co-located. In their study in which 4,514 persons were screened for HCV infection at 5 different federally qualified health centers, Coyle et al reported that the most successful linkage-to-care rate was seen at the one health center in which HCV testing, care, and treatment were provided in the same setting [67.6% (167 out of 247)] [20]. The high percentage of persons linked to care in this study is likely due to both the continuing relationship of the participants with the WTCGRC Research Study and the co-location of the Mount Sinai Liver Medicine Practice.

This is the first well-designed epidemiologic study to suggest an association between contact with sewage and HCV infection. A study in 1999 described two sewer workers with no recognized HCV risk factors and routine skin contact with sewer water, who were diagnosed with HCV infection [21]. A cross-sectional study of 19,503 persons in Brazil, ages 10 to 69, from all 26 State capitals and the Federal District, found that families without public sewage disposal had an increased risk of HCV infection [OR=2.53, 95% CI (1.38, 4.65)] after adjusting for age, IDU, use of sniffed drugs, injection with a glass syringe, and hospitalization [22]. The authors interpreted this finding as an association between HCV infection and low socioeconomic status, and did not discuss the possibility of contact with sewage as a risk factor for HCV infection.

There are few HCV seroprevalence studies among persons with occupational contact with sewage. A study of 107 sanitary workers in Pakistan, ages 20 to 48, with at least five years of exposure to opening drains, large sewage ducts, and sewage piping, found 39 (36%) had HCV antibodies [23]. This was higher than the prevalence of HCV infection in the general population of Pakistan (2.6%-5.3%). A study of 410 sanitary workers in Alexandria, Egypt, found 9.8% had HCV antibodies [24]. This was similar to the estimated prevalence of HCV infection in the region's general population. However, generalizing findings from this Egyptian study is difficult. Egypt has a history of mass spread of HCV infection during a campaign to fight schistosomiasis, which was followed by mass treatment for infected persons and mass education campaigns to prevent further spread [25].

The association between contact with sewage and HCV infection may not be real. There are well-established risk factors for which this study was unable to adjust, including household contacts with HCV infection [12], sexual risk behaviors [13], and level of education [14], because our questionnaire did not capture this information. However, it is not clear how exposure to sewage at the WTC site would correlate with these unmeasured risk factors. Additionally, some may question the validity of an association with a P-value of 0.05 found in this analysis. However, a P-value ≤ 0.05 is the generally accepted level by which statistical significance is measured, the one used for this study design, and, therefore, the one we must follow in interpreting our results.

In this study, work as a truck driver was associated with an increased risk of HCV infection and work at perimeter security was associated with a decreased risk of HCV infection. The association between work as a truck driver and increased risk of HCV infection is consistent with previous research [26]; this consistency provides validation for this study. The decreased risk of HCV infection among persons working at perimeter security may suggest distance from the site was protective against HCV infection. This may lend further support to an increased risk of HCV infection when exposed to sewage at the site.

While the association between HCV infection and contact with sewage has not been widely reported, this association is biologically plausible. A cross-sectional study of 98 stool samples without occult blood from 98 persons with chronic HCV infection, found 68 (69%) had detectable HCV RNA [27]. Similarly, a cross-sectional study of 12 stool samples from 12 persons with chronic HCV infection, found 10 (83%) had detectable HCV RNA [28]. Ciesek et al found HCV RNA infectivity in a liquid environment lasted up to 5 months at lower temperatures (4 °C) and up to 21 days at room temperature (21 °C) [29]. Paintsil et al found that an HCV clone dried on fomite surfaces maintained its infectivity for up to 6 weeks at 4 °C and 22 °C [30]. Thus, WTCGRC members who reported sewage contact may have come into contact with infective HCV RNA and acquired HCV infection through breaks in their skin or mucous membranes.

This study did not find associations between contact with human remains and/or blood and bodily fluid, and HCV infection. The OSHA requirements for the use of protective gear when contacting these substances [5, 6] has likely increased worker awareness of their danger and may have led to self-protective behaviors, like avoidance of these substances when possible and washing hands immediately after contact.

There are several limitations to this study. Most importantly, the WTCGRC baseline questionnaire did not clearly define what constitutes “contact with sewage” allowing responders individual interpretations. However, given the lack of knowledge of most responders about their HCV status at the time they completed the baseline questionnaire, such misclassification would have been non-differential, leading to an underestimate of the association between contact with sewage and HCV infection. Because some participants enrolled in the WTCGRC Research Study many years after the WTC events, there may be misclassification of exposure due to difficulties with recall. Here to, it is likely that the misclassification would have been non-differential, leading to an underestimate of the association between contact with sewage and HCV infection. This study is unable to determine when HCV infection occurred. IDU is closely associated with HCV infection and participants may not report past IDU. However, it is unlikely that IDU use is correlated with contact with sewage at the WTC site, and, therefore, missing data on IDU is unlikely to confound the relationship between sewage and HCV infection. There are some unmeasured confounders in this study including occupation before and after WTC.

5. Conclusions

This study suggests that existing cohort studies may serve as venues for HCV screening and linkage to care. More research is needed on the relationship between contact with sewage and HCV infection. The combination of the current nested case-control study and the cross-sectional study of HCV in Brazil [22] suggests that contact with sewage may be a risk factor for HCV in persons with occupational contact with sewage and persons with non-occupational contact with sewage. The CDC now recommends that all adults in the US, ages 18 and over, get tested for HCV at least once in their lifetime [31]. Additional research is needed to determine if the association we detected is real and whether additional HCV screening is appropriate for persons with ongoing contact with sewage.

Supplementary Materials: The following are available in the online version: Table S1: Data sources for nested case-control study, Figure S1: Prevalence of hepatitis C virus antibodies by year of birth in members of the World Trade Center General Responder Cohort and the US population, Table S2: Association between participant activity at the World Trade Center site and hepatitis C virus antibody status, Table S3. Characteristics of World Trade Center (WTC) perimeter security workers from a subset of the WTC General Responder Cohort, recruited and tested for hepatitis C virus antibodies from December 15, 2016 – July 12, 2018 (N=520), Table S4. Characteristics of World Trade Center (WTC) truck drivers from a subset of the WTC General Responder Cohort, recruited and tested for HCV from December 15, 2016 – July 12, 2018 (N=24).

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Declaration of Interest: Douglas T. Dieterich is a consultant and speaker for Gilead and AbbVie. The other authors declare no conflicts of interest.

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