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ACUTE NON-A-E HEPATITIS IN THE UNITED STATES AND THE ROLE OF HEPATITIS G VIRUS INFECTION

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ABSTRACT

Background Little is known about the relation of the newly discovered hepatitis G virus (HGV) to the cause and clinical course of acute and chronic viral hepatitis.

Methods We selected patients from a surveillance study of acute viral hepatitis in four U.S. counties who had acute disease during 1985 to 1986 or 1991 to 1995. Serum samples were tested for HGV RNA by the polymerase chain reaction.

Results HGV RNA was detected in 4 of 45 patients with a diagnosis of non-A-E hepatitis (9 percent), 23 of 116 patients with hepatitis C (20 percent), 25 of 100 patients with hepatitis A (25 percent), and 32 of 100 patients with hepatitis B (32 percent) ($P < 0.05$ for the comparison of hepatitis B with hepatitis non-A-E or C). The clinical characteristics of the acute illness were similar for patients with HGV alone and those with hepatitis A, B, or C with or without HGV infection. During a follow-up period of one to nine years, chronic hepatitis did not develop in any of the patients with HGV alone, but 75 percent were persistently positive for HGV RNA, as were 87 percent of those with both hepatitis C and HGV infection. The rates of chronic hepatitis were similar in patients with hepatitis C alone (60 percent) and those with both hepatitis C and HGV infection (61 percent).

Conclusions The evidence from this surveillance study does not implicate HGV as an etiologic agent of non-A-E hepatitis. Persistent infection with HGV was common, but it did not lead to chronic disease and did not affect the clinical course in patients with hepatitis A, B, or C. (N Engl J Med 1997;336:741-6.)

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ABOUT 10 to 15 percent of patients with parenterally transmitted non-A, non-B hepatitis have no evidence of hepatitis C virus (HCV) infection after extensive evaluation and can therefore be classified as having non-A-E hepatitis.¹⁻⁴ As compared with patients with acute hepatitis C, patients with acute non-A-E hepatitis are less likely to be jaundiced, have lower peak alanine aminotransferase levels, and have a lower frequency of chronic hepatitis (0 to 29 percent).^{1,3,4}

Recently, two isolates of a new virus, designated hepatitis GB virus C or hepatitis G virus (HGV), were identified from patients with viral hepatitis.⁵⁻⁷ The amino acid sequences of the two isolates are 95 percent homologous, and the genomic organization of this virus places it in the family Flaviviridae, which includes HCV.^{6,7} Because no antigenic epitopes have been identified that can be used to develop a serologic test that detects current infection, studies of HGV infection are dependent on polymerase-chain-reaction (PCR) techniques.

To determine the characteristics of acute non-A-E hepatitis in the United States and the possibility that it is caused by HGV, we analyzed data from patients with acute, clinically apparent viral hepatitis who were identified through a sentinel surveillance system involving counties in four states since 1982.^{1,8,9}

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METHODS

Enrollment

The Sentinel Counties Study of Viral Hepatitis enrolls all patients with acute viral hepatitis reported to the county health departments involved in the study: Jefferson County (Birmingham), Alabama; Denver County (Denver), Colorado; Pinellas County (St. Petersburg), Florida; and Pierce County (Tacoma), Washington.^{1,8,9} The current study included a subgroup of patients identified during two time periods who were at least 18 years old and had serum samples available for testing: all patients with acute non-A, non-B hepatitis during 1985 to 1986 who participated in a prospective study of the natural history of the disease,¹ and all patients with acute non-A, non-B hepatitis during 1991 to 1995 as well as a sample of 100 consecutively identified patients with acute hepatitis A and 100 with acute hepatitis B during this period. The groups with hepatitis A and B were balanced to include the same proportion of injection-drug users as that found among all the patients with hepatitis C.

Clinical criteria for inclusion in the study were a physician's diagnosis of acute viral hepatitis that was based on the discrete onset of signs and symptoms, serum aminotransferase activity that was more than 2.5 times the upper limit of normal, and the exclusion of other causes of liver disease.^{1,8} Serum samples were collected from all patients within six weeks after the onset of illness. Hepatitis A was defined by the presence of IgM antibody against hepatitis A virus (HAV); hepatitis B by the presence of both hepatitis B surface antigen and IgM antibody against hepatitis B core antigen or of IgM antibody against hepatitis B core antigen; and hepatitis C by the presence of antibody against HCV (anti-HCV), HCV RNA, or antibody against HCV native antigens in the initial or follow-up serum samples obtained from patients negative for IgM antibody against HAV and hepatitis B core antigen.^{1,10} Patients who were negative for all these viral hepatitis markers (non-A, non-B, non-C hepatitis) were then tested for antibody against hepatitis E virus (HEV), and all were negative, defining this group as having non-A-E hepatitis. All the patients were interviewed to identify risk factors for hepatitis during the six months preceding the onset of illness.^{1,8,9}

Follow-up

For the cohort of patients with hepatitis C or non-A-E hepatitis identified during 1985 to 1986 who provided written informed consent, serum samples were collected beginning six months after the onset of acute illness, every three months thereafter for four years, and then yearly for up to nine years. A subgroup of these patients underwent clinical evaluation for chronic liver disease, including liver biopsy.¹ For the cohort of patients with hepatitis C or non-A-E hepatitis identified during 1991 to 1995 who provided written informed consent, serum samples were collected beginning six months after the onset of acute illness and every six months thereafter for up to three years. All follow-up samples were tested for alanine aminotransferase activity and markers of HAV, hepatitis B virus (HBV), and HCV infection. Chronic hepatitis was defined as a finding of two or more abnormal alanine aminotransferase values at least nine months after the onset of acute illness.¹

Laboratory Studies

Serum samples were tested with commercially available radioimmunoassays (Abbott Laboratories, North Chicago, Ill.) for hepatitis B surface antigen, antibody against hepatitis B core antigen, and antibody against hepatitis B surface antigen and enzyme immunoassays (Abbott Laboratories) for IgM antibody against HAV, IgM antibody against hepatitis B core antigen, and anti-HCV (a second-version assay was used). Samples negative for anti-HCV were retested by a third-version enzyme immunoassay (Ortho Diagnostic Systems, Raritan, N.J.).¹¹ Samples that were repeatedly reactive for anti-HCV with the use of either assay were tested by the appropriate supplemental anti-HCV assay (Matrix HCV, Abbott Laboratories, or RIBA 3.0, Chiron, Emeryville, Calif.). Test-

ing by reverse-transcriptase PCR for HCV RNA and by fluorescent-antibody blocking for antibody against HCV native antigens was carried out as described previously.^{1,10} Testing for antibody against HEV was performed with an enzyme immunoassay that detects antibodies against capsid proteins.¹²

Available serum samples (initial and follow-up) from patients with hepatitis C or non-A-E hepatitis were tested for HGV RNA after nucleic acid amplification by reverse-transcriptase PCR. RNA was extracted from 100 μ l of serum with a guanidinium-isothiocyanate-acid phenol procedure (RNAzol, Biotecx Laboratories, Houston) and reverse-transcribed with Moloney murine leukemia virus with primer 211R located in nonstructural region 5 (NS5) of the HGV genome.⁷ The resulting complementary DNA was amplified for 45 cycles with primers 211R and 77F as previously reported,⁷ and the specificity of the PCR products was confirmed by Southern blot hybridization with a ³²P-labeled probe (5'CTCCATCGCCAGCACTTATCTCGGTAC3'). To monitor each run, human serum samples found to be negative for HGV RNA on at least five occasions were tested in duplicate to check for cross-contamination, and the sensitivity was assessed by the inclusion of an end-point dilution series of the cloning-source plasma.⁷ Samples that tested negative with NS5 primers were retested with primers located in the 5' untranslated region (UTR-1F: 5'GTAGGTCGTAATCCCGGTCAC3', and UTR-1R: 5'CCCACTGGTCCTTGCAACTCG3'), and products were confirmed by hybridization with a ³²P-labeled probe (5'GTCTCTCTTGACCAATAGGCGTAGCCG3').

Serum samples from patients with acute hepatitis A or hepatitis B were tested for HGV RNA by reverse-transcriptase PCR, and PCR products were detected fluorogenically (TaqMan, Perkin-Elmer, Applied Biosystems, Foster City, Calif.) by methods used to detect HCV RNA.¹³ Briefly, reverse-transcriptase PCR was performed with the primers for the NS5 region described above, and the PCR product was detected spectrophotometrically (model LS50 luminescent spectrometer, Perkin Elmer) with a probe synthesized with the reporter dye 6-carboxyfluorescein covalently attached to the 5' end and the quencher dye 6-carboxy-tetramethyl-rhodamine attached by a linker downstream from the 6-carboxyfluorescein.

Statistical Analysis

Frequency distributions were compared with the two-tailed Mantel-Haenszel chi-square test or two-tailed Fisher's exact test, and means were compared with Student's t-test. Stratified and logistic-regression analyses were performed to control for confounding variables. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

A total of 10,533 patients with acute viral hepatitis were reported to the Sentinel Counties surveillance system during 1982 to 1995: 5033 had hepatitis A (48 percent; 95 percent confidence interval, 47 to 49 percent), 3598 had hepatitis B (34 percent; 95 percent confidence interval, 33 to 35 percent), 1580 had hepatitis C (15 percent; 95 percent confidence interval, 15 to 16 percent), and 322 had non-A-E hepatitis (3 percent; 95 percent confidence interval, 2.7 to 3.4 percent).

HGV Infection in Patients with Acute Non-A-E Hepatitis or Hepatitis C

During the two periods selected for this study (1985 to 1986 and 1991 to 1995), serum samples were available for HGV testing from 45 of 98 patients identified as having acute non-A-E hepatitis

(46 percent) and 116 of 266 patients identified as having acute hepatitis C (44 percent). HGV RNA was detected in 4 patients with non-A-E hepatitis (9 percent) and 23 patients with hepatitis C (20 percent). There was no difference in the prevalence of HGV infection between the two time periods, although all four patients with HGV infection alone were identified in 1985.

The demographic and clinical characteristics of these patients were compared on the basis of their HGV status (Table 1). The patients with HGV infection alone were younger (all but one were less than 30 years old), but their acute clinical characteristics were similar to those of the patients with HCV alone or those infected with both HCV and HGV. Three of the four patients with HGV infection alone were jaundiced, and three (including one without jaundice) had other nonspecific symptoms of viral hepatitis (fatigue, nausea, and loss of appetite). The patients with no evidence of infection with a known hepatitis virus (non-A-G) were older and had milder acute disease with significantly lower alanine aminotransferase activity, but they were more likely to be hospitalized for their acute illness ($P < 0.05$, adjusted for age).

HGV Infection in Patients with Hepatitis A or B

HGV RNA was detected in 25 of 100 patients with hepatitis A (25 percent) and 32 of 100 patients

with hepatitis B (32 percent). The prevalence of HGV infection was significantly higher among patients with hepatitis B than among patients with hepatitis C or non-A-E hepatitis ($P < 0.05$). Most (70 to 80 percent) of the HGV infections occurred in persons younger than 40 years old. The clinical characteristics of patients with HGV and either hepatitis A or hepatitis B were similar to those of patients with hepatitis A or B alone (data not shown).

Clinical Outcome of Patients with HGV Infection

During a follow-up period of one to nine years, no biochemical evidence of chronic hepatitis developed in the four patients with HGV infection alone (Table 1). In contrast, chronic hepatitis developed in 60 percent of the patients with HCV infection and in a similar proportion (61 percent) of the patients with both HCV and HGV infections. Chronic hepatitis also developed in 32 percent of the group with non-A-G hepatitis. HGV infection persisted in 75 percent of the group infected with HGV alone and in 87 percent of the group infected with both HCV and HGV. In both groups of patients, detection of HGV RNA was intermittent, with two or more negative determinations preceded and followed by positive determinations.

Only nine of the patients with persistently abnormal alanine aminotransferase levels in this study had

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WITH ACUTE NON-A, NON-B HEPATITIS ACCORDING TO THEIR HGV AND HCV INFECTION STATUS.

CHARACTERISTIC	HGV ALONE (N=4)	HCV ALONE (N=93)	HCV AND HGV (N=23)	NON-A-G (N=41)	CHI-SQUARE*	P VALUE
Age — no. (%)					7.70	0.05
<40 yr	4 (100)	63 (68)	18 (78)	21 (51)		
≥40 yr	0	30 (32)	5 (22)	20 (49)		
Median — yr	27	34	31	39		
Range — yr	16–39	18–80	19–97	20–83		
Sex — no. (%)					5.03	0.17
Male	2 (50)	36 (39)	14 (61)	22 (54)		
Female	2 (50)	57 (61)	9 (39)	19 (46)		
Race — no. (%)					7.51	0.06
White	1 (25)	68 (73)	17 (74)	23 (56)		
Nonwhite	3 (75)	25 (27)	6 (26)	18 (44)		
Alanine aminotransferase level ≥16 times the upper level of normal — no. (%)	3 (75)	66 (71)	17 (74)	12 (29)	23.15	<0.001
Median — U/liter	1680	1410	1673	335	—	<0.01
Range — U/liter	200–3240	122–7375	630–2630	179–4410		
Bilirubin — mg/dl†						
Median	9.6	4.1	4.5	3.6	—	>0.05
Range	0.6–30.9	0.5–25.5	0.8–18.6	0.4–18.7		
Hospitalized for acute illness — no. (%)	1 (25)	15 (16)	3 (13)	14 (34)	6.61	0.08
Chronic hepatitis — no. (%)‡	0	50 (60)	14 (61)	12 (32)	13.24	<0.01
Persistent HGV infection — no. (%)	3 (75)	—	20 (87)	—		

*A two-by-four table of comparison was used, with 3 df.

†To convert values to micromoles per liter, multiply by 17.1.

‡Only 84 of the patients with HCV alone and 38 of those with non-A-G hepatitis were followed for at least nine months.

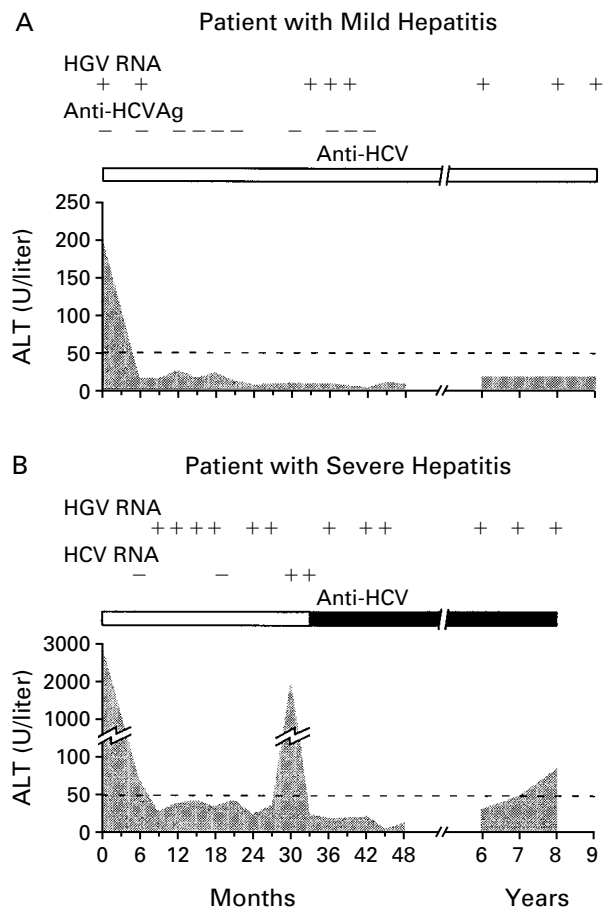


Figure 1. HGV Infection and the Clinical Course of Hepatitis. Panel A shows the clinical course of a patient with mild acute illness with complete biochemical resolution of hepatitis but the persistence of HGV RNA. Panel B shows the course of a patient with relatively severe illness that was slow to resolve. This patient was initially positive for HGV RNA alone. Plus signs indicate the presence of HGV RNA or HCV RNA, and minus signs indicate the absence of detectable HGV RNA, HCV RNA, or antibody against HCV native antigens (anti-HCVAg). The open bar indicates the absence of antibody against HCV (anti-HCV), and the solid bar its presence. The dashed line shows the upper limit of normal values for alanine aminotransferase (ALT).

undergone liver biopsy. In the HCV-infected group, five patients (one of whom was also infected with HGV) had mild hepatitis, and one patient (with HCV infection alone) had cirrhosis. In the group with non-A–G hepatitis, two patients had mild hepatitis and one had chronic active hepatitis. Because all the patients with HGV infection alone had persistently normal alanine aminotransferase activity, none had undergone liver biopsy.

The typical clinical course of a patient with HGV infection alone is shown in Figure 1A. This patient had a relatively mild acute illness with complete biochemical resolution of hepatitis, whereas assays for HGV RNA remained positive for nine years. The pa-

tient whose course is shown in Figure 1B had a relatively severe illness, with slowly resolving hepatitis, and initially was positive for HGV RNA alone. During follow-up, HGV RNA was detected in all samples tested, whereas alanine aminotransferase activity remained normal until 30 months after the initial illness. At that time the patient had a second episode of acute hepatitis, during which HCV RNA was detected, followed by the appearance of anti-HCV. Alanine aminotransferase activity again returned to normal for more than five years, when it increased to a level of 86 U per liter, suggesting the presence of chronic hepatitis presumably due to HCV infection.

Potential Sources of Infection

Factors present in the six months before the onset of illness that are known to be associated with a risk of acquiring non-A, non-B hepatitis^{8,14} were evaluated with the use of mutually exclusive categories in the patients with HGV alone, HCV alone, HCV and HGV, and non-A–G hepatitis (Table 2). Transfusion-associated hepatitis occurred among patients in all groups. Injection-drug users were found in all of the groups except the group with non-A–G hepatitis. One patient with HGV infection alone had a history of multiple sex partners. The group with non-A–G hepatitis had a disproportionate number of patients who denied having most of the risk factors; for most of these patients, the only distinguishing characteristic was low socioeconomic level. Evidence of prior HBV infection was found more often in patients infected with HCV alone or with HCV and HGV than in patients with HGV infection alone ($P > 0.05$) or patients with non-A–G hepatitis ($P < 0.01$) (Table 2).

When analyses were stratified according to injection-drug use, there was a significantly higher prevalence of HGV infection among the drug users with hepatitis A or hepatitis B than among patients with hepatitis A or B who reported no use of injection drugs (Table 3). We found no such difference for patients with hepatitis C (even after multivariate analysis), although in all three groups, at least 40 percent of the HGV infections were among injection-drug users.

DISCUSSION

The epidemiologic data obtained from sentinel surveillance for acute viral hepatitis in the four counties have been shown to be representative of the United States with respect to clinically overt viral hepatitis.^{8,9} If the data from this study are applied to all cases of acute viral hepatitis identified during the past 14 years, they suggest that approximately 0.3 percent (95 percent confidence interval, 0.2 to 0.4 percent) of persons with acute viral hepatitis may be infected with HGV alone. However, this study did not implicate HGV as an etiologic agent of non-A–E

TABLE 2. FACTORS ASSOCIATED WITH A RISK OF NON-A, NON-B HEPATITIS IN THE SIX MONTHS BEFORE THE ONSET OF ILLNESS AMONG THE PATIENTS, ACCORDING TO THEIR HGV AND HCV INFECTION STATUS.

FACTOR*	HGV ALONE (N=4)	HCV ALONE (N=93)	HGV AND HCV (N=23)	NON-A-G (N=41)
	no. of patients (%)			
Blood transfusion	1 (25)	18 (19)	4 (17)	4 (10)
Injection-drug use	1 (25)	34 (37)	10 (43)	0
Employment in health care field	0	3 (3)	0	0
High-risk sexual behavior†	1 (25)	7 (8)	0	2 (5)
Other high-risk behavior‡	0	14 (15)	4 (17)	1 (2)
Low socioeconomic level	1 (25)	11 (12)	4 (17)	20 (49)
Unknown§	0	6 (6)	1 (4)	14 (34)
Prior HBV infection	0	31 (33)	7 (30)	4 (10)

*All categories are mutually exclusive except prior HBV infection.

†This category includes sexual contact with someone who had a history of hepatitis or who was positive for anti-HCV or exposure to multiple sexual partners.

‡This category includes a history of the following: injection-drug use more than six months before the onset of illness, sexual or household contact with someone who injected drugs, use of illegal non-injection drugs, imprisonment, or sexually transmitted diseases other than hepatitis.

§The patients denied having any risk factors.

hepatitis. Although there was a high proportion of injection-drug users among the patients with hepatitis A, B, or C, the proportion of patients with non-A-E hepatitis who were found to be positive for HGV RNA was similar to or lower than that of patients with other types of viral hepatitis, even when injection-drug users were excluded. Published case series have claimed an association between HGV and acute and chronic liver disease as well as fulminant hepatitis,^{7,15,16} but case-control studies are required to confirm whether or not HGV is an etiologic agent of viral hepatitis or any other disease. However, the ability to carry out such studies is limited by the small number of patients with HGV infection alone.

The data from this study suggest that HGV may not be primarily a hepatotropic agent; instead, it may induce hepatitis only under certain circumstances, as is observed with other viruses (e.g., cytomegalovirus and yellow fever virus). That HGV does not replicate primarily in the liver is supported by the absence of disease in chimpanzees that were intravenously inoculated with HGV¹⁷ and by data from prospective studies of transfusion recipients showing that rates of HGV infection are similar among persons in whom hepatitis develops and those in whom it does not.¹⁸

The presence of HGV infection had no apparent effect on the clinical course of acute disease among the patients with hepatitis A, B, or C or on the frequency and severity with which chronic hepatitis developed in patients with hepatitis C, a finding con-

TABLE 3. PREVALENCE OF HGV INFECTION AMONG PATIENTS WITH ACUTE HEPATITIS A, B, OR C, ACCORDING TO INJECTION-DRUG USE.

TYPE OF HEPATITIS	TOTAL	DRUG USE	NO DRUG USE	P VALUE
	no. positive for HGV RNA/total no. (%)			
A	25/100 (25)	15/31 (48)*	10/69 (14)	<0.001
B	32/100 (32)*	15/29 (52)*	17/71 (24)	<0.05
C	23/116 (20)	10/44 (23)	13/72 (18)	>0.05
Total	80/316 (25)	40/104 (38)	40/212 (19)	<0.001

*P<0.05 for the comparison with hepatitis C.

firmed by other studies.¹⁹ Most patients with HGV infection had viremia for long periods, but none of the patients with HGV infection alone had biochemical evidence of chronic hepatitis. However, our sample was small and included only patients with clinically apparent disease, so we cannot draw definitive conclusions regarding the course and outcome of all persons infected with HGV alone.

Although the association of HGV with disease remains unclear, there is no question that HGV is a unique virus that can be transmitted by blood.^{7,17,18} In addition to transmission by transfusion or experimental inoculation, there have been reports of presumed blood-borne transmission of HGV from infected women to their newborns and possibly among

patients on hemodialysis.²⁰⁻²² We cannot draw conclusions about risk factors for acquiring HGV infection, both because of the small number of patients with HGV infection alone in the study and because only patients with disease were included as controls. However, in this and other studies, HGV infection appeared to be acquired at younger ages than other known types of viral hepatitis,¹⁹ and of the patients with HGV infection alone, only one reported injection-drug use and none had evidence of prior exposure to HBV. In addition, the high prevalence of HGV infection among patients with hepatitis A or B who had no history of drug use raises the possibility that other routes of transmission for HGV may be important.

Persistent infection with HGV appears to be quite prevalent in the general population, with almost 2 percent of blood donors⁷ and 14 to 52 percent of patients with other types of viral hepatitis being positive for HGV RNA. Since blood donors are a highly selected group, they are not representative of the general population and the estimated prevalence of HGV in this group, as of HBV and HCV infection,^{23,24} probably represents the lower end of the range, just as estimates of prevalence among patients with viral hepatitis who have high-risk behavior probably represent the upper end.

The cause of acute non-A-E viral hepatitis in the United States remains unknown, and in this study the characteristics of patients in this group were distinctly different from those of patients with known types of viral hepatitis. The patients were older, had milder illness, were more likely to be hospitalized for their hepatitis independent of their age, and had few identifiable sources of disease. The heterogeneous nature of the demographic, clinical, and epidemiologic characteristics of this group suggests that there are multiple etiologic factors, some of which may not be viral.

APPENDIX

The following are other members of the Sentinel Counties Viral Hepatitis Study Team: M. Fleenor, T. Greene, S. Hill, F. Judson, J. Kaluba, B. Laird, S. Lambert, R. Massie, C. Miron, K. Mottram, O. Nainan, B.R. Pixley, K. Schomer, J. Shaw, G. Tillman, L. Wafer, and I. Williams.

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