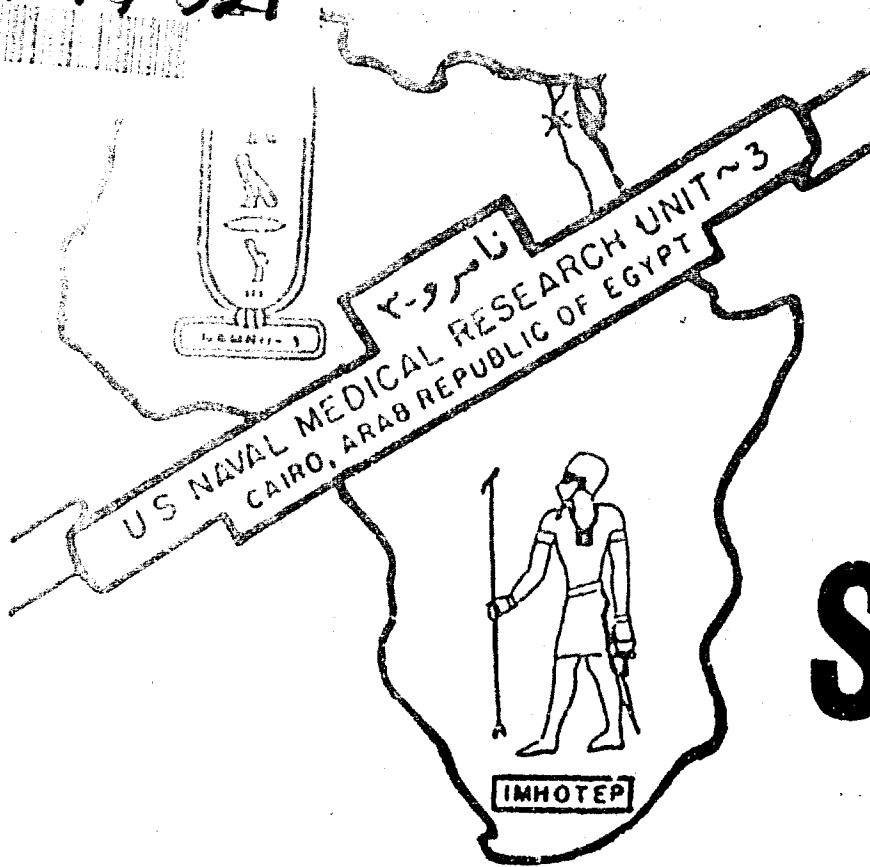


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# PUBLICATION REPORT

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1771

5/94

PREVALENCE OF HEPATITIS C VIRAL ANTIBODY IN  
 TRANSFUSED AND NONTRANSFUSED EGYPTIAN CHILDREN

BY

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94-14367

94 5 13 025

# REPORT DOCUMENTATION PAGE

Form Approved  
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY (leave blank)		2. REPORT DATE <p style="text-align: center;">1993</p>		3. REPORT TYPE AND DATES COVERED	
4. TITLE AND SUBTITLE <b>Prevalence of Hepatitis C Viral Antibody in Transfused and Non-transfused Egyptian Children</b>				5. FUNDING NUMBERS PE- 62770A WU- 3M162770A870.AR.322	
6. AUTHOR(S) <b>Khalifa, A.S., Mitchell, B.S., Watts, D.M., El-Samahy, M.H., El-Sayed, M.H., Hassan, N.F., Jennings, G.B., Hibbs, R.G. and Corwin, A.L.</b>					
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) <b>U.S. Naval Medical Research Unit No. 3 PSC 452, Box 5000 FPO AE 09835-0007</b>				8. PERFORMING ORGANIZATION REPORT NUMBER <p style="text-align: center;">5/94</p>	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) <b>Naval Medical Research and Development Command, National Naval Medical Center Building 1, Tower 12 Bethesda, MD 20889-5044</b>				10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES  <p style="text-align: center;">Published in: Am. J. Trop. Med. Hyg., <u>49</u>(3):316-321, 1993; Acc. No. 1771.</p>					
12a. DISTRIBUTION/AVAILABILITY STATEMENT  <p style="text-align: center;">Approved for public release; Distribution is unlimited.</p>				12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words)  <p>Hepatitis C (HCV) virus is recognized as the major cause of what was previously referred to as parenterally acquired (blood-mediated) non-A, non-B hepatitis. A study involving 252 transfused and nontransfused Egyptian children was conducted from November 1990 through February 1991 to determine the prevalence of HCV and the role of blood and blood and blood product transfusions in the spread of the virus. Serum specimens were assayed by a second generation enzyme immunoassay and were considered reactive only after supplemental testing using the second generation recombinant immunoblot assay. Prevalence among 84 young study subjects with hematologic disorders was 55% (46 of 84), while no HCV antibodies were detected among the two nonhematologic pediatric populations studied: 84 hospital admissions and 84 acutely ill but otherwise healthy outpatients (seeking treatment for symptoms associated with a new condition less than three weeks old in the absence of any chronic health problem). Ninety-two percent (77 of 84) of the hematology-related cases had medical histories of multiple transfusions. Positive antibody responses (46) were significantly associated with increased duration of illness (<math>P &lt; 0.001</math>) and the volume and number of transfusions (<math>P &lt; 0.01</math>) when compared with negative ones (38). However, prior hospitalization and/or surgery were not related to HCV antibody status. The high prevalence of HCV antibody among multiply transfused infants and children suggests that blood and blood product supplies should be regularly screened for HCV antibody.</p>					
14. SUBJECT TERMS <b>Hepatitis C virus; Prevalence; Blood transfusions; Blood products; Serology; Transfused children; Nontransfused children; Egypt.</b>				15. NUMBER OF PAGES <p style="text-align: center;">6</p>	
17. SECURITY CLASSIFICATION OF REPORT <p style="text-align: center;">UNCLASSIFIED</p>				16. PRICE CODE	
18. SECURITY CLASSIFICATION OF THIS PAGE <p style="text-align: center;">UNCLASSIFIED</p>		19. SECURITY CLASSIFICATION OF ABSTRACT <p style="text-align: center;">UNCLASSIFIED</p>		20. LIMITATION OF ABSTRACT	

## PREVALENCE OF HEPATITIS C VIRAL ANTIBODY IN TRANSFUSED AND NONTRANSFUSED EGYPTIAN CHILDREN

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**Abstract.** Hepatitis C (HCV) virus is recognized as the major cause of what was previously referred to as parenterally acquired (blood-mediated) non-A, non-B hepatitis. A study involving 252 transfused and nontransfused Egyptian children was conducted from November 1990 through February 1991 to determine the prevalence of HCV and the role of blood and blood and blood product transfusions in the spread of the virus. Serum specimens were assayed by a second generation enzyme immunoassay and were considered reactive only after supplemental testing using the second generation recombinant immunoblot assay. Prevalence among 84 young study subjects with hematologic disorders was 55% (46 of 84), while no HCV antibodies were detected among the two nonhematologic pediatric populations studied: 84 hospital admissions and 84 acutely ill but otherwise healthy outpatients (seeking treatment for symptoms associated with a new condition less than three weeks old in the absence of any chronic health problem). Ninety-two percent (77 of 84) of the hematology-related cases had medical histories of multiple transfusions. Positive antibody responses (46) were significantly associated with increased duration of illness ( $P < 0.001$ ) and the volume and number of transfusions ( $P < 0.01$ ) when compared with negative ones (38). However, prior hospitalization and/or surgery were not related to HCV antibody status. The high prevalence of HCV antibody among multiply transfused infants and children suggests that blood and blood product supplies should be regularly screened for HCV antibody.

Most cases of blood-associated viral hepatitis, including that of community-acquired (sporadic) infections in the absence of non-hepatitis B (HBV) can be attributed to hepatitis C virus (HCV) infections.<sup>1,2</sup> A particularly high prevalence of HCV has been found among many European populations with chronic liver disease.<sup>3</sup> In Taiwan, HCV infection was found in 43% and 63% of hepatitis B surface antigen (HBsAg)-negative patients with cirrhosis and hepatocellular carcinoma, respectively, although prevalence among HBsAg-positive patients with chronic liver disease was significantly lower.<sup>4</sup>

Hepatitis C virus has been shown to be the most common cause of post-transfusion hepatitis. Risk groups include dialysis patients and hemophiliacs. Parenteral transmission has been implicated as the major route in the spread of hepatitis C.<sup>1,3</sup> In Taiwan, HCV prevalence was 90% among screened hemophiliacs and 81% among parenteral drug abusers, compared with 1% among voluntary blood donors.<sup>4</sup>

Few data are available concerning HCV prevalence in young children, particularly from North Africa. Findings from healthy adult blood donors working in Saudi Arabia showed that HCV antibody prevalence rates among Egyptians (19.2%) were significantly higher than those of Saudis (1.3%), Sudanese (1.9%), and Yemenis (2.4%).<sup>5</sup> In this report, we present findings on the prevalence rates of HCV antibodies in transfused and nontransfused Egyptian children.

### MATERIALS AND METHODS

#### *Subjects*

Two hundred fifty-two children from the Children's Hospital of Ain Shams University in Cairo, Egypt were studied between November 1990 and February 1991 for the presence of antibodies to HCV. Their ages ranged from six months to 15 years (mean 6.9 years). Three risk classifica-

tions relative to HCV transmission were represented among the study populations.

Group 1 was composed of 84 consecutively selected outpatient cases seen in the Pediatric Hematology/Oncology Clinic with hematologic disorders that included beta-thalassemia major (24), thalassemia intermedia (three), sickle thalassemia (three), acute leukemias (24), hemophilia A (10), hemophilia B (two), idiopathic thrombocytopenia purpura (ITP) (eight), hypoplastic anemias (five), autoimmune hemolytic anemia (three), and hereditary spherocytosis (two). Their mean  $\pm$  SD age was  $7 \pm 3.7$  years.

Group 2 was composed of 84 consecutively selected hospitalized admissions with nonhematologic ailments such as rheumatic diseases, diabetes mellitus, renal disorders, and respiratory diseases. Their mean  $\pm$  SD age was  $7.4 \pm 4$  years.

Group 3 was composed of 84 consecutively selected children who were seen for acute problems that consisted mainly of acute respiratory infections and enteric-related conditions at the hospital's outpatient clinic. Their mean  $\pm$  SD age was  $6.2 \pm 3.7$  years.

### Methods

Informed consent was obtained from a parent or legal guardian who accompanied the child to the hospital prior to inclusion in the study. A standardized questionnaire was completed for all study subjects. This provided an epidemiologic profile and medical history with an emphasis on the presence or absence of suspected risk factors associated with HCV transmission. Additional information from children admitted to the hospital with and without hematologic disorders was obtained from hospital records. Data and specimen collection procedures were approved by the Naval Medical Research Unit No. 3 Committee for the Protection of Human Subjects.

A thorough clinical examination was conducted to note the presence or absence of clinical jaundice, liver span, and the size of the spleen. Serum samples were also tested for an elevated level of alanine transaminase (ALT) (550 Express; Ciba-Corning Diagnostics Corp., Medfield, MA). A normal ALT level for this assay was  $< 30$  IU per liter. Samples were also tested for total bilirubin (550 Express; Ciba-Corning Diagnostics Corp.) and an HBsAg enzyme-linked

immunosorbent assay (ELISA) (Abbott Laboratories, North Chicago, IL).

Testing of sera for HCV antibodies was carried out at the U.S. Naval Medical Research Unit No. 3, in Cairo, Egypt. All ELISA testing was initially carried out using a second generation HCV enzyme immunoassay (Abbott Laboratories). Patient sera were incubated with polystyrene beads coated with recombinant (*Escherichia coli* or yeast) HCV antigens. At the end of the test, samples with absorbance values greater than or equal to the cutoff value were considered initially reactive. If positive results were obtained upon retesting of the sample, the specimen was considered positive for HCV antibodies. Samples that twice showed a positive reaction for HCV antibodies were then supplementally tested using a recombinant immunoblot assay (RIBA) (Chiron, Emeryville, CA). The antigens C33-C, C22-3, 5-1-1, and C100-3 and superoxide dismutase were present in bands on nitrocellulose strips. Following incubation of serum samples with the nitrocellulose strips, antigen band intensities were compared with weakly positive (level I) and moderately positive (level II) IgG control bands. A response of 1+ or greater (up to 4+) to two or more HCV antigens was interpreted as a positive result, a response to one antigen was interpreted as indeterminate, and no response to any antigen bands was interpreted as a negative result. Indeterminate results were considered negative for the purpose of study analysis.

### RESULTS

Clinical findings from both histories and clinical examinations showed that the hematologic subjects (group 1) presented with a significantly more intensive medical profile (percentages) relative to prior hospitalization and surgery, personal and family history of jaundice, and ALT values  $> 30$  IU compared with nonhematologic study populations (groups 2 and 3). Ninety-six percent (81 of 84) of study participants in group 1 had a history of prior blood only transfusions; 95% (77 of 81) of these had had more than one such transfusion. Also evident was the absence of any history (both documented and reported) of blood only transfusions among children in groups 2 and 3. The mean ALT level was significantly higher among subjects in group 1 compared with values found

TABLE 1

Prevalence of hepatitis C virus (HCV) antibodies by group and hematologic classification, November 1990 through February 1991\*

	Group 1 % (No. positive/ no. tested)	Group 2 % (No. positive/ no. tested)	Group 3 % (No. positive/ no. tested)
HCV-2 EIA†	69 (58/84)	1 (1/84)	2 (2/84)
RIBA‡	79 (46/58)	0 (0/1)	0 (0/2)
Thalassemias‡	73 (22/30)		
Acute leukemias‡	25 (6/24)		
Hemophilias‡	83 (10/12)		
ITP‡	50 (4/8)		
Hypoplastic anemias‡	60 (3/5)		
Hereditary spherocytosis‡	0 (0/2)		
Autoimmune anemia‡	33 (1/3)		

\* For a definition of the groups, see Subjects and Methods. EIA = enzyme immunoassay; RIBA = recombinant immunoblot assay; ITP = idiopathic thrombocytopenia purpura.

† Repeat positive (twice positive) using second generation EIA.

‡ Tested by second generation RIBA; all repeat positives (twice positive) were tested by second generation EIA.

in groups 2 and 3 ( $P < 0.001$ ). Similarly, the percentage of subjects with an ALT level greater than 30 IU/l was significantly higher than for the other two groups ( $P < 0.001$ ).

The proportion of pediatric hematology-related cases with HCV antibodies in group 1 was 55% (46 of 84) (Table 1). No antibody to HCV was detected in either groups 2 or 3. In each of the seven hematologic disorders represented in group 1, except for those with hereditary spherocytosis, HCV antibody-positive subjects were identified. Notable was the high prevalence

among children and infants classified as thalassemias (73%) and hemophilias (83%).

Reactivity to HCV among group 1 study subjects was associated with prolonged duration of illness (Table 2). Children with HCV antibodies had a significantly higher mean duration (in years) of illness than those with no detectable antibody ( $P < 0.001$ ), regardless of age. The mean volume of blood only transfusions was significantly higher among seropositive individuals than among seronegative ones ( $P < 0.01$ ). Similarly, the mean number of blood only transfusions was greater among seropositive study subjects, although not significantly ( $P > 0.05$ ). Children with evidence of HCV had a significantly higher mean number of transfusions when blood products and blood were factored together ( $P < 0.001$ ).

The clinical data in Table 3 show that HCV-positive cases had significantly larger spleens ( $P < 0.01$ ) and livers ( $P < 0.05$ ) than their seronegative counterparts. A higher proportion of children with antibodies to HCV also presented with clinical jaundice ( $P < 0.01$ ). Laboratory findings showed that seropositive subjects had higher bilirubin levels ( $P < 0.05$ ), but there was no evidence that ALT levels were significantly associated with HCV antibody prevalence. However, when acute leukemias were excluded from the calculation of mean ALT values, the level in children positive for antibodies to HCV was significantly higher than in negative ones ( $P < 0.05$ ). The presence of HBsAg was detected in both positive and negative HCV cases, with the prevalence being notably higher among seronegative individuals ( $P < 0.05$ ).

TABLE 2

Age, sex, and reported and documented medical histories, by hepatitis C virus (HCV) antibody reactivity (+ or -) determined by enzyme immunoassay and recombinant immunoblot assay, in group 1 patients, November 1990 through February 1991

	HCV nega- tive (n = 38)	HCV posi- tive (n = 46)
Mean (years)	6	8
Sex (M:F)	55:45	60:40
Mean duration of illness (years)	2	4*
History of jaundice (%)	29	37
Family history of jaundice (%)	5	7
History of surgery (%)	18	22
History of hospitalization (%)	79	74
Mean volume (ml) of transfusions with blood only	3,725	4,336†
No. of transfusions with blood only (mean units)	12	18†
No. of transfusions with blood and blood products (mean units)	12	27*

\*  $P < 0.001$ .

†  $P < 0.01$ .

TABLE 3

Clinical features and laboratory findings, by hepatitis B virus (HCV) antibody reactivity (+ or -) in group 1 patients, November 1990 through February 1991\*

	HCV negative (n = 38)	HCV positive (n = 46)
<b>Clinical features</b>		
Clinical jaundice (%)	5	22†
Mean liver span (cm)	7 (5-11)	8‡ (5-15)
Mean spleen size (cm)	2 (0-14)	4 (0-15)†
<b>Laboratory results</b>		
Bilirubin (direct) (mg/dl)	0.07 (0.0-0.25)	0.12‡ (0.0-1.2)
Mean ALT, IU/l	38 (5-155)	34‡ (5-137)
Mean ALT, IU/l‡	20	34‡
HBsAg carrier (%)	19‡	7

\* Values in parentheses are ranges. ALT = alanine transaminase; HBsAg = hepatitis B surface antigen.

†  $P < 0.01$ .

‡  $P < 0.05$ .

§ Mean ALT value excluding cases of acute leukemias.

Table 4 shows a corresponding increase in the prevalence of HCV antibodies and the increased cumulative volume of blood only transfusions. The absolute percent difference (APD) between transfusion levels  $< 1,200$  ml and  $\geq 1,200$  ml but  $\leq 4,000$  ml (19%) did not differ significantly. However, the percentage of HCV antibody-positive cases at the  $> 4,000$  ml level (71%) was significantly higher ( $P < 0.01$ ) than at the  $< 1,200$  ml level (37%). The risk of infection was also linked with the cumulative number of blood only transfusions received. The APD between  $< 4$  times and  $> 12$  times (34%) varied significantly ( $P < 0.01$ ).

#### DISCUSSION

The prevalence (55%) of HCV antibodies found among hematology-related cases, 92% (77 of 84) of whom had a history of multiple transfusions, was higher than seroconversion results reported from Swedish and American transfusion recipients.<sup>6,7</sup> This finding is notable in that no antibodies were detected by RIBA among the nonhematologic pediatric controls ( $n = 168$ ).

The prevalence of HCV among Egyptian children with hemophilia (83%) was similar to that reported from Taiwan (90%), Sweden (87%), and Germany (80%).<sup>4,8,9</sup> High HCV antibody prevalence was also found among other study subjects with hematologic disorders that included thalassemias (73%), hypoplastic anemias (60%), and ITP (50%). In contrast, prevalence estimates of HCV antibody in patients with thalassemias in the United States and Greece were 15% and 29%.

respectively (Kostaridou S and others, unpublished data).

Prolonged duration of illness was significantly ( $P < 0.001$ ) associated with HCV positivity among patients with hematologic disorders. Clearly, the number of transfusions required is more likely to increase with the length of illness. Similarly, the mean values pertaining to the volume (blood only) and number (blood only and blood and blood products) of transfusions were significantly higher ( $P < 0.01$ ) for seropositive subjects. These data are further strengthened by the finding of a parallel between increased prevalence and increased levels (volume) and numbers of blood only transfusions, as shown in Table 4.

Alanine transaminase has been used as a surrogate marker of non-A, non-B hepatitis

TABLE 4

Risk-associated with increased number and volume of blood only transfusions, by hepatitis C virus (HCV) antibody reactivity (+ or -) in group 1 patients, November 1990 through February 1991\*

	HCV positive % (No. positive/ no. tested)
<b>Transfusion level (blood only)</b>	
$< 1,200$ ml	37 (11/30)
$\geq 1,200$ ml- $\leq 4,000$ ml	56 (14/25)
$> 4,000$ ml	71 (20/28)
<b>No. of transfusions (blood only)</b>	
$< 4$	41 (12/29)
$\geq 4$ - $\leq 12$	44 (10/23)
$> 12$	75 (21/28)

\*  $P = 0.028$  for transfusion level and 0.019 for no. of transfusions, by chi-square test.

(NANBH).<sup>2, 7, 10</sup> The mean ALT level of HCV-positive individuals was significantly higher than for seronegative individuals only after cases of acute leukemias were excluded from the comparison. This phenomenon may be attributed to the chemotherapy nominally administered for acute leukemias, namely methotrexate. This contrasts with other reports that suggest that NANBH, and not drug hepatotoxicity, is the primary cause of hypertransaminemia in children with acute lymphoblastic leukemia.<sup>11, 12</sup> Meanwhile, ALT screening should be of value in identifying donors in the window period before seroconversion, those with aberrant antibody responses that are not detected by the current assay, and those infected with NANBH agents other than HCV.<sup>13, 14</sup>

In conclusion, these data are consistent with the recognized role of transfusions with blood only or blood and blood products as an important vehicle in the spread of HCV. Familial transmission of antibody to HCV via mother to child was not apparent; otherwise, had it been present or occurred, there would have been evidence of HCV infection in young children with no hematologically related disorders. Positivity was dependent on the duration of illness, and more importantly, transfusion history, regardless of age. Mothers of study subjects, however, were not screened for antibodies to HCV. Future studies should involve the screening of family members.

Screening of all blood and blood products for NANBH, particularly HCV, should be considered in Egypt. Furthermore, persons with hematologically related disorders would benefit from periodic monitoring for chronic hepatic disease progression.

**Acknowledgment:** We give special thanks to Kenneth C. Hyams (U.S. Naval Medical Research Institute, Bethesda, MD) for consultations and editorial review of the manuscript.

**Financial support:** This study was supported by U.S. Naval Medical Research and Development Command Work Unit No. 3M162770.A870.AR.322.

**Disclaimer:** The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or as reflecting the views of U.S. Navy or the Department of Defense.

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Reprint requests: Publications Office, U.S. Naval Medical Research Unit No. 2, Box 3, Unit 8132, APO AP 96520-8132.

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