Hepatitis C Virus Prevalence and Clearance among US Blood Donors, 2006–2007: Associations with Birth Cohort, Multiple Pregnancies, and Body Mass Index

Edward L. Murphy, Junyong Fang, Yongling Tu, Ritchard Cable, Christopher D. Hillyer, Ronald Sacher, Darrell Triulzi, Jerome L. Gottschall, and Michael P. Busch, for the Retrovirus Epidemiology Donor Study

1University of California, San Francisco, and 2Blood Systems Research Institute, San Francisco, California; 3Westat, Rockville, Maryland; 4American Red Cross Blood Services, New England Division, Farmington, Connecticut; 5Emory University and 6American Red Cross Blood Services, Southern Region, Atlanta, Georgia; 7Hoxworth Blood Center, Cincinnati, Ohio; 8Institute for Transfusion Medicine, Pittsburgh, Pennsylvania; and 9Blood Center of Wisconsin, Milwaukee, Wisconsin

Background. During the period 1992–1993, the prevalence of hepatitis C virus (HCV) antibodies (anti-HCV) among US blood donors was 0.36%, but contemporary data on the prevalence of antibody to HCV and the prevalence of HCV RNA are lacking.

Methods. We performed a large, cross-sectional study of blood donors at 6 US blood centers during 2006–2007. Anti-HCV was measured with enzyme-linked immunosorbent assay followed by immunoblot, and HCV RNA was measured with nucleic acid testing. Adjusted odds ratios (aORs) were derived using multivariable logistic regression.

Results. Of 959,281 donors, 695 had anti-HCV detected (prevalence, 0.072%). Of those with anti-HCV, 516 (74%) had test results positive for HCV RNA, and 179 (26%) had test results that were negative for HCV RNA. Compared with the prevalence during the period 1992–1993, prevalence during 2006–2007 was lower and peaked in older age groups. Anti-HCV was associated with a body mass index (BMI) ≥ 30 (aOR, 0.6; 95% confidence interval [CI], 0.5–0.8), and among women, it was associated with higher gravidity (aOR for ≥10 vs 0 pregnancies, 3.2; 95% CI, 1.9–5.4). HCV RNA negative status was associated with black race (aOR, 0.4; 95% CI, 0.2–0.7), having more than a high school education (aOR, 1.6; 95% CI, 1.1–2.4), and BMI ≥ 30 (aOR, 2.4; 95% CI, 1.4–3.9).

Conclusions. Decreasing HCV prevalence is most likely attributable to culling of seropositive donors and a birth cohort effect. We found new associations between anti-HCV prevalence and gravidity and obesity. Recently discovered genetic factors may underlie differences in HCV RNA clearance in black donors.

Hepatitis C virus (HCV) is a blood-borne virus that causes chronic hepatitis, cirrhosis, and hepatocellular carcinoma and has recently been implicated in the pathogenesis of non-Hodgkin’s lymphoma [1, 2]. More than 170 million people worldwide are positive for antibodies to HCV (anti-HCV), with prevalences of 1%–2% in most populations, although prevalences are occasionally much higher because of instances of iatrogenic infection. In the United States, prevalence is 1.6% in the general population, with the highest prevalence among men and those 40–49 years of age [3]. In US blood donors, prevalence was estimated at 0.36% in the early 1990s, again with the highest prevalence in males and middle-aged donors [4]. One study showed a significant decrease in HCV prevalence among first-time US blood donors from 0.63% in 1991 to 0.40% in 1996, whereas another showed an overall decrease in HCV...
prevalence but an increase among men 50–59 years of age [5, 6]. The incidence among repeat blood donors is low, and since

the institution of nucleic acid testing (NAT) for HCV RNA in

1999, which allowed the discovery and quarantine of early anti-

body-negative “window period” blood units, the residual risk

of HCV infection has been estimated to be 1 in 1.8 million

blood units transfused [7].

However, recent data on HCV prevalence and risk factors

among a large sample of US blood donors are lacking. Such
data are important to understand the burden of infection in
different donor subgroups and to predict future prevalence
for public health purposes. From an epidemiologic standpoint, it
has been postulated that HCV infection in the United States
demonstrates a birth cohort effect because of an epidemic of
transmission by injection drug use in the 1960s and 1970s [4].
If such an effect could be proven by showing a reduced pre-
valence in more contemporary data, it would have important
implications for modeling the future burden of HCV infection
in the United States and the health care impact of HCV-related
disease outcomes. Current parallel testing of blood donors for
anti-HCV and HCV RNA also allows the investigation of the
determinants of presumptively resolved HCV infection as man-
ifested by anti-HCV–positive but HCV RNA–negative status.

We therefore performed a large, cross-sectional prevalence
study of HCV prevalence among blood donors at a research
network of 6 blood centers throughout the United States. Data
were compared with those from an earlier published study from
a similar US blood center network [4], and a separate analy-
sis of the determinants of HCV RNA–positive or HCV RNA–
negative status was undertaken.

METHODS

Study population and design. This was a cross-sectional se-

roprevalence study conducted among blood donors at 6 US

blood centers from January 2006 through September 2007. The

blood centers participated in the Retrovirus Epidemiology

Donor Study II and included American Red Cross Blood Ser-

vices, New England (Vermont, New Hampshire, Maine and

Massachusetts) and Southern (Georgia) regions, the Institute

for Transfusion Medicine (Pennsylvania), the Hoxworth Blood

Center (Ohio), the Blood Center of Wisconsin (Wisconsin),

and Blood Centers of the Pacific (California). Computerized
data on all blood donations during the study period was for-

warded to the coordinating center and merged into a central
research database. Each blood donor was represented only once
in the data presented here; the donor was considered to be
positive if any donation during the study period had positive
test results. First-time and repeat donors were defined as those
who had or did not have, respectively, a record of previous
donation at that center. Body mass index (BMI), calculated as
weight in kilograms divided by the square of height in meters,

was categorized as normal (<25), overweight (25–29.99), or

obese (≥30). All anti-HCV–positive donors were notified and

excluded from future donation according to blood center op-

erational protocols. Data collection was performed under pro-
tocols approved by institutional review boards at the 6 partic-
ipating blood centers.

HCV testing. For the prevalence analysis, HCV infection

was defined as the presence of anti-HCV (positive enzyme-
linked immunosorbent assay [EIA] result followed by a positive
recombinant immunoblot result). For the analysis of chronic
versus resolved HCV infection, the results from parallel NAT
were used to sort anti-HCV–positive subjects into persistently
viremic (HCV RNA–positive) and presumptively resolved or
resolving (HCV RNA–negative) HCV infections. All laboratory
testing was done using US Food and Drug Administration–
licensed assays and under strict standard operating proce-
dures at the blood center laboratories. Anti-HCV was mea-
sured with third-generation EIAs; recombinant immunoblot
confirmation was done either on all EIA-positive samples (5
centers) or on EIA-positive samples that were NAT negative (1
center), and this had no effect on proportions of confirmed
anti-HCV between centers. NAT was done with either tran-
scription-mediated amplification (Genprobe/Novartis; pools of
16) or polymerase chain reaction (Roche Laboratories; pools
of 24) techniques.

Statistical analysis. We calculated overall and subgroup-
specific anti-HCV and HCV RNA prevalences with 95% con-
fidence intervals (CIs) using the Clopper-Pearson method [8].
Distributions of BMI were compared between HCV status groups
using analysis of variance (ANOVA). Three separate multivariable
logistic regression models were constructed and used to calculate
adjusted odds ratios (aORs) and 95% CIs. In the first, the prev-
ance analysis included all HCV-screened donors and tested
associations between anti-HCV positivity and donor character-
istics, irrespective of RNA status. A second prevalence model
examining gravidity was similar to the former model but was
restricted to female subjects only. In the third model, the analysis
of resolved versus chronic HCV infection included anti-HCV–
positive individuals only and tested associations of HCV RNA–
negative status with various donor characteristics. We used a
backward-elimination strategy in constructing each multivariable
model. All variables were included in the initial model; those
variables without associations (P > .10) were then excluded from
the final model unless forced in because of biological plausibility
or previously published findings.

RESULTS

We reviewed 959,281 donors, of whom 695 (72 per 100,000)
had evidence of HCV infection, including 516 (74%) with both
anti-HCV and HCV RNA positivity and 179 (26%) with anti-
HCV positivity only. Subgroup-specific prevalence and aORs
are presented in Table 1. Anti-HCV prevalence was much higher among first-time donors than it was among repeat donors and was higher among male donors than among female donors. Age-specific prevalence increased to a maximum in the 40–49 and 50–59-year-old age groups and decreased thereafter. Prevalence was lower in 2006–2007 than it was in 1992–1993 in all age and sex groups (Figure 1) [4], and peak prevalence shifted to older age groups. Prevalence was highest among blacks, was similar in non-Hispanic whites and Hispanics, and was lowest among Asians.

In the multivariable logistic regression model for anti-HCV prevalence (Table 1), we found significant, independent associations between anti-HCV positivity and middle age, male sex, and black versus non-Hispanic white race/ethnicity. Donors with Asian race/ethnicity were significantly less likely to be anti-HCV positive. Significant associations were also seen with high

Table 1. Prevalence of Hepatitis C Virus (HCV) Antibodies (anti-HCV) among Blood Donors and Adjusted Odds Ratio (aOR) for the Association with Each Variable

<table>
<thead>
<tr>
<th>Donor group</th>
<th>No. of donors</th>
<th>No. of anti-HCV–positive donors</th>
<th>Prevalence of anti-HCV positivity per 100,000 donors</th>
<th>aOR (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First time donor</td>
<td>280,612</td>
<td>631</td>
<td>225</td>
<td>38.3 (29.1–50.4)</td>
</tr>
<tr>
<td>Repeat donor</td>
<td>675,294</td>
<td>57</td>
<td>8</td>
<td>1.0</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>179,427</td>
<td>45</td>
<td>25</td>
<td>0.1 (0.1–0.2)</td>
</tr>
<tr>
<td>20–29</td>
<td>158,617</td>
<td>82</td>
<td>52</td>
<td>1.0</td>
</tr>
<tr>
<td>30–39</td>
<td>141,220</td>
<td>102</td>
<td>72</td>
<td>2.0 (1.5–2.7)</td>
</tr>
<tr>
<td>40–49</td>
<td>199,592</td>
<td>246</td>
<td>123</td>
<td>4.3 (3.3–5.5)</td>
</tr>
<tr>
<td>50–59</td>
<td>178,893</td>
<td>191</td>
<td>107</td>
<td>4.7 (3.6–6.2)</td>
</tr>
<tr>
<td>≥60</td>
<td>101,526</td>
<td>29</td>
<td>29</td>
<td>1.2 (0.8–1.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>467,996</td>
<td>415</td>
<td>89</td>
<td>1.8 (1.6–2.1)</td>
</tr>
<tr>
<td>Female</td>
<td>491,255</td>
<td>279</td>
<td>57</td>
<td>1.0</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>810,716</td>
<td>531</td>
<td>65</td>
<td>1.0</td>
</tr>
<tr>
<td>Black</td>
<td>56,467</td>
<td>78</td>
<td>138</td>
<td>1.4 (1.1–1.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>34,722</td>
<td>24</td>
<td>69</td>
<td>0.7 (0.5–1.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>22,351</td>
<td>8</td>
<td>36</td>
<td>0.5 (0.2–0.9)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>265,874</td>
<td>312</td>
<td>117</td>
<td>8.1 (6.2–10.5)</td>
</tr>
<tr>
<td>Some College</td>
<td>281,132</td>
<td>219</td>
<td>78</td>
<td>3.8 (2.9–4.9)</td>
</tr>
<tr>
<td>College graduate</td>
<td>327,961</td>
<td>74</td>
<td>23</td>
<td>1.0</td>
</tr>
<tr>
<td>Ever received transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>815,780</td>
<td>503</td>
<td>62</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>31,252</td>
<td>54</td>
<td>173</td>
<td>2.1 (1.6–2.8)</td>
</tr>
<tr>
<td>Body mass indexb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight/normal (&lt;25)</td>
<td>342,961</td>
<td>213</td>
<td>62</td>
<td>1.0</td>
</tr>
<tr>
<td>Overweight (&gt;30)</td>
<td>314,378</td>
<td>240</td>
<td>76</td>
<td>0.9 (0.7–1.1)</td>
</tr>
<tr>
<td>Obese (&gt;30)</td>
<td>218,965</td>
<td>156</td>
<td>71</td>
<td>0.6 (0.5–0.8)</td>
</tr>
<tr>
<td>Blood center</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wisconsin</td>
<td>122,071</td>
<td>48</td>
<td>39</td>
<td>1.0</td>
</tr>
<tr>
<td>California</td>
<td>90,462</td>
<td>78</td>
<td>86</td>
<td>3.6 (2.3–4.9)</td>
</tr>
<tr>
<td>Georgia</td>
<td>250,759</td>
<td>234</td>
<td>93</td>
<td>2.8 (2.0–3.9)</td>
</tr>
<tr>
<td>Ohio</td>
<td>70,521</td>
<td>34</td>
<td>48</td>
<td>2.2 (1.4–3.3)</td>
</tr>
<tr>
<td>Massachusetts, Vermont, New Hampshire, and Maine</td>
<td>303,740</td>
<td>202</td>
<td>67</td>
<td>2.5 (1.8–3.4)</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>121,728</td>
<td>99</td>
<td>81</td>
<td>2.8 (2.0–4.0)</td>
</tr>
</tbody>
</table>

NOTE. Reference categories are indicated by an aOR of 1.0.

a Statistically significant association.
b Body mass index was calculated according to the weight in kilograms divided by the square of the height in meters.
school or lower education, previous blood transfusion, and blood center, and an inverse association was seen with BMI. Among female donors only, anti-HCV prevalence increased with the number of pregnancies. Thirty individuals were anti-HCV positive per 100,000 donors (57 of 192,518) among nulligravida women, 57 were positive per 100,000 donors (27 of 47,523) among women with 1 pregnancy, 71 were positive per 100,000 donors (122 of 171,795) among women with 2–4 pregnancies, and 144 per 100,000 (29 of 20,072) in women with ≥5 pregnancies. In a separate multivariable model with female donors only and including previous transfusion and race/ethnicity along with age, BMI, educational attainment, blood center, and first-time versus repeat donor status, women with multiple pregnancies were significantly more likely to be anti-HCV positive (aOR for 1 pregnancy, 1.3 [95% CI, 0.8–2.1]; aOR for 2–4 pregnancies, 1.6 [95% CI, 1.1–2.4]; aOR for ≥5 pregnancies, 3.2 [95% CI, 1.9–5.5]; all vs nulligravida women). Country of birth and blood donation procedure were eliminated from the final model because of a lack of statistical significance. Further analyses excluding repeat donors did not substantially change the results reported above.

We next evaluated associations with HCV RNA status among anti-HCV–positive donors (Table 2). A total of 516 anti-HCV–positive donors had HCV RNA detected, and 179 did not; an additional 24 donors with incident HCV infection (HCV RNA positive but anti-HCV negative) were excluded from further analysis. HCV RNA–negative status was less likely to be detected among donors of black race/ethnicity. However, HCV RNA–negative status was positively associated with greater than high school education, obesity (defined as a BMI ≥30), and donation at the Georgia blood center. Female sex was not significantly associated with HCV RNA status (aOR, 1.09; 95% CI, 0.74–1.60), but it and other covariates were retained in the model because of prior reports in the literature and/or concern regarding potential confounding factors. Further analyses excluding repeat donors did not substantially change the results reported above.

Because of the above-noted inverse associations of BMI with anti-HCV and HCV RNA positivity, a graph of the frequency distribution of BMI according to anti-HCV and HCV RNA status is shown in Figure 2. It shows that the entire distribution of BMI is shifted significantly to the right for anti-HCV–positive, HCV RNA–negative donors, compared with both anti-HCV–positive, HCV RNA–positive donors and anti-HCV–negative, HCV RNA–negative donors (P = .008, by ANOVA). Anti-HCV–positive, HCV RNA–negative donors are both less likely to be thin and more likely to be overweight or obese than are the other 2 groups.

**DISCUSSION**

Compared with results from a decade and a half earlier, this study provides additional evidence that anti-HCV prevalence is decreasing among US blood donors, most likely because of culling of seropositive individuals, as well as because of a birth cohort effect. In addition, we describe new associations of anti-HCV prevalence with increasing number of pregnancies among women and with lower BMI among all donors. Finally, HCV RNA–negative status was less likely to be observed among black donors and was more likely to be observed among better educated and obese donors.

The decrease in HCV prevalence in the current analysis, compared with prevalence reported in a similar study for 1992–1993 [4], is consistent with that seen in other studies of blood donors in the United States and Canada [5, 6, 9]. Over this time, there has been little if any change in donor eligibility criteria. We and others have previously proposed a birth cohort effect for HCV infection among North American blood donors as explaining decreasing prevalence, because donors in the birth cohort at highest risk for HCV infection (those born from the late 1940s through the early 1960s), who have the highest lifetime prevalence of injection drug use [10], are progressively less represented among active blood donors [4, 6, 9]. The current data, which shows lower age-specific prevalence in all age groups together with a shift in the maximum prevalence to donors who are a decade older, compared with the 1992–1993 data, supports the birth cohort hypothesis, as well as culling...
<table>
<thead>
<tr>
<th>Variable</th>
<th>Anti-HCV–positive donors (n = 695)</th>
<th>No. (%) of anti-HCV–positive, HCV RNA–negative donors (n = 179)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td>--------------</td>
</tr>
<tr>
<td>&lt;20</td>
<td>45</td>
<td>6 (13)</td>
<td>1.00</td>
</tr>
<tr>
<td>20–29</td>
<td>82</td>
<td>20 (24)</td>
<td>1.44 (0.5–4.1)</td>
</tr>
<tr>
<td>30–39</td>
<td>102</td>
<td>29 (28)</td>
<td>1.58 (0.6–4.4)</td>
</tr>
<tr>
<td>40–49</td>
<td>246</td>
<td>60 (24)</td>
<td>1.49 (0.6–3.9)</td>
</tr>
<tr>
<td>≥50</td>
<td>220</td>
<td>64 (29)</td>
<td>2.03 (0.8–5.4)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>415</td>
<td>102 (25)</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>279</td>
<td>76 (27)</td>
<td>1.09 (0.7–1.6)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
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<td></td>
</tr>
<tr>
<td>White</td>
<td>531</td>
<td>146 (27)</td>
<td>1.00</td>
</tr>
<tr>
<td>Black</td>
<td>78</td>
<td>13 (17)</td>
<td>0.37 (0.2–0.7)</td>
</tr>
<tr>
<td>Other</td>
<td>131</td>
<td>29 (22)</td>
<td>1.39 (0.7–2.8)</td>
</tr>
<tr>
<td>US born</td>
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</tr>
<tr>
<td>Yes</td>
<td>591</td>
<td>156 (26)</td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>26</td>
<td>6 (23)</td>
<td>0.89 (0.3–2.5)</td>
</tr>
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<td>Education</td>
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<tr>
<td>High school or less</td>
<td>312</td>
<td>68 (22)</td>
<td>1.00</td>
</tr>
<tr>
<td>Some college or higher</td>
<td>293</td>
<td>89 (30)</td>
<td>1.61 (1.1–2.4)</td>
</tr>
<tr>
<td>Center</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wisconsin</td>
<td>48</td>
<td>9 (19)</td>
<td>1.00</td>
</tr>
<tr>
<td>California</td>
<td>78</td>
<td>17 (22)</td>
<td>0.96 (0.4–2.5)</td>
</tr>
<tr>
<td>Georgia</td>
<td>234</td>
<td>76 (32)</td>
<td>2.71 (1.2–6.1)</td>
</tr>
<tr>
<td>Ohio</td>
<td>34</td>
<td>7 (21)</td>
<td>1.07 (0.3–3.3)</td>
</tr>
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<td>Massachusetts, Vermont, New Hampshire, Maine</td>
<td>202</td>
<td>43 (21)</td>
<td>1.07 (0.5–2.4)</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>99</td>
<td>27 (27)</td>
<td>1.69 (0.7–4.1)</td>
</tr>
<tr>
<td>Donor status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-time donor</td>
<td>631</td>
<td>158 (25)</td>
<td>1.00</td>
</tr>
<tr>
<td>Repeat donor</td>
<td>57</td>
<td>19 (33)</td>
<td>1.28 (0.7–2.4)</td>
</tr>
<tr>
<td>Donation type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole blood donation</td>
<td>660</td>
<td>168 (25)</td>
<td>1.00</td>
</tr>
<tr>
<td>Other procedure</td>
<td>35</td>
<td>11 (31)</td>
<td>1.24 (0.6–2.8)</td>
</tr>
<tr>
<td>History of receipt of transfusion</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>503</td>
<td>132 (26)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>54</td>
<td>15 (28)</td>
<td>0.95 (0.5–1.9)</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight/normal (&lt;25)</td>
<td>213</td>
<td>42 (20)</td>
<td>1.00</td>
</tr>
<tr>
<td>Overweight (25–30)</td>
<td>240</td>
<td>61 (25)</td>
<td>1.36 (0.8–2.2)</td>
</tr>
<tr>
<td>Obese (&gt;30)</td>
<td>156</td>
<td>56 (36)</td>
<td>2.36 (1.4–3.9)</td>
</tr>
</tbody>
</table>

**NOTE.** Resolved HCV infection was defined as the presence of anti-HCV without HCV RNA positivity. Numbers may not add to totals because of missing values for some variables. Reference categories are indicated by an aOR of 1.0. anti HCV, antibodies to HCV; aOR, adjusted odds ratio; CI, confidence interval.

- Statistically significant association.
- Body mass index was calculated according to the weight in kilograms divided by the square of the height in meters.

of seropositive donors since the introduction of HCV testing in the early 1990s. Similar indications of a birth cohort effect may be seen in US and Japanese general population data [3, 11, 12]. Confirmation of a birth cohort effect is important, because it implies that HCV prevalence in the United States will likely continue to decrease over upcoming decades. The generation born in the late 1940s through the early 1960s will likely manifest the peak incidence of HCV disease outcomes.
of cirrhosis and hepatocellular carcinoma, with decreasing rates in subsequent generations.

Our finding of an association of HCV prevalence with increasing gravidity is novel and of potential public health concern if substantiated by other studies. In favor of the validity of this association is the apparent dose effect with increasing number of pregnancies and its persistence despite adjustment for potential confounding by age, previous transfusion history, race/ethnicity, and education. In light of the weight of evidence against sexual intercourse as a major transmission route of HCV, we do not believe the pregnancy association is a surrogate for sexual transmission [13]. Antenatal care and childbirth are accompanied by medical injections, instrumentation, and a high proportion of cesarian births that could be opportunities for iatrogenic transmission of HCV. Women in our study could also have received transfusions during surgical procedures or while under anesthesia without remembering the event. The hypothesis of iatrogenic exposure is supported by the findings of a case control study of HCV infection among pregnant women in Karachi, Pakistan, which found aORs of 1.25 for 3–4 pregnancies and 1.99 for ≥5 pregnancies. Those authors concluded that iatrogenic exposures during delivery could be the source of infection [14].

We could find no published US studies to suggest iatrogenic transmission in the obstetric setting, although a large outbreak of HCV infection has recently been attributed to unsafe injection practices at a Las Vegas endoscopy clinic [15]. A review article counted 33 outbreaks in nonhospital health care settings in the past decade: 12 in outpatient clinics, 6 in hemodialysis centers, and 15 in long-term care facilities, resulting in 448 persons acquiring HBV or HCV infection [16]. Thus, the hypothesis of a low-level iatrogenic risk may be plausible and ought to be examined by other studies. Finally, in this cross-sectional study, we cannot rule out residual confounding, perhaps by age or socioeconomic status, as contributing to the observed association.

Our analysis of HCV nucleic acid status found that presumptive clearance of HCV RNA was less likely in black subjects and more likely in those with higher educational status and obesity; no statistically significant association was found between the sexes in the multivariable analysis. The association with black race/ethnicity is consistent with a number of reports in the literature and may be attributable to genetic differences in human leukocyte antigen type or interleukin 18 promoter polymorphism [1, 17, 18]. Polymorphism in the IL28b gene has recently been proposed as a major determinant of racial differences in both treatment response and spontaneous clearance of HCV viremia [19–22]. The association of HCV clearance with higher educational status was not found in the previous cross-sectional analysis among blood donors [23]. Better access to health care and antiviral treatment among donors with higher socioeconomic status seems unlikely to explain this effect, because most donors were presumably unaware of their HCV status at the time of donation. Our lack of an association of female sex with HCV clearance adds to a divided literature on this topic. Several studies with and without adjustment for potential confounding factors have found that anti-HCV–positive women are more likely to be HCV RNA negative than are their male counterparts [24–27], and a prospective study involving young injection drug users observed a higher incidence of clearance among females subjects [28]. However, 3 other studies that included subjects who were US injection drug users, US blood donors, and members of the Italian general population found no significant association of HCV clearance with sex [1, 5, 29, 30]. Because the latter studies generally showed a reduction in odds ratios from univariate to multivariable
analysis, it is conceivable that observed associations with sex may be confounded by route of infection or risk group. In addition, the disappearance of anti-HCV, which occurs slowly after resolution of viremia, could lead to differential underestimation of “ever infected” status in cross-sectional studies.

Another novel result of the study is that donors with higher BMI were less likely to have anti-HCV, and among those who had results positive for anti-HCV, those with higher BMI were less likely to test positive for HCV RNA. These findings were somewhat counterintuitive, because the literature implies that chronic infection with HCV may induce a “metabolic syndrome” that includes insulin intolerance and hepatic steatosis [31]. Similarly, patients with HCV infection who are also obese tend to have a higher risk of progression to high-grade fibrosis [32], perhaps because of increased inflammatory markers observed in patients who are both HCV positive and obese [33, 34]. Obesity is also a risk factor for hepatocellular carcinoma, both with and without HCV infection [35]. On the other hand, a study that specifically excluded obese subjects and those with hepatic steatosis found no effect of HCV infection on insulin resistance [36]. A recent large population-based study in Taiwan, which had findings that were perhaps most similar to our own results, found that anti-HCV positive subjects tended to have lower levels of both cholesterol and triglycerides [37]. Perhaps the key to reconciling these conflicting observations is to separate studies that involve generally healthy populations, such as blood donors, for whom obesity may have a protective effect against HCV infection, from studies involving patients with liver disease, for whom obesity and HCV infection may represent co-morbidities. One study suggested an underlying genetic explanation for these observations, finding that low-density lipoprotein receptor polymorphisms may modulate immune response to HCV [38]. Alternatively, an inflammatory state including macrophage infiltration of fat pads and increased production of interleukin 6 and tumor necrosis factor α has recently been linked to obesity and could contribute to the resolution of HCV infection [39, 40].

Finally, a significantly higher prevalence of HCV clearance at one of the blood centers was a puzzling result. One hypothesis is that this was attributable to differences in HCV genotype. Higher prevalences of the anti-HCV–positive, HCV RNA–negative state have been reported from countries with genotypes other than type 1 [41, 42]. On the other hand, younger injection drug users in San Francisco, California, had a higher ratio of HCV genotype 3 to genotype 1 than did older injection drug users, but the incidence of HCV clearance did not differ by genotype [28]. Blood donors in the southern United States had the highest incidence of new, anti-HCV–negative, HCV RNA–positive HCV infections but did not show more non–type 1 HCV genotypes [43]. This suggests another possible explanation for higher proportions of HCV RNA–negative status in Georgia. Most HCV RNA clearance occurs within the first year of infection [28] and may be followed by the disappearance of anti-HCV over a period of several years [44]. Therefore, a higher incidence of new HCV infections at our Georgia center during the time frame of the study could lead to oversampling of resolving infections in individuals who had lost HCV RNA but had not yet lost anti-HCV, compared with a center with lower incidence, where most infections would be in individuals with long-term HCV RNA positivity.

Strengths of the current study include its large size and representation of generally healthy blood donors from several blood centers across the United States. All anti-HCV and HCV RNA testing was performed in parallel and with state-of-the-art assays under the rigorous quality control typical of blood center laboratories. Weaknesses include the cross-sectional design, which does not allow true determination of cause and effect, and the possibility of residual confounding of reported associations by measured and unmeasured variables. Although blood center HCV RNA testing performed on individual samples is generally more sensitive than assays used in the clinic [45], there may be some misclassification of HCV RNA status because of testing in pools of 16 or 24 instead of testing undiluted specimens, although this effect has been shown to be small [46, 47]. Finally, although we believe blood donors are more comparable to the general population than are hospital or clinic patients with HCV infection, conclusions derived from blood donors may not be directly applicable to the general population or to other patients because of selection for better health.

In conclusion, this study provides additional evidence that HCV infection prevalence has decreased substantially among blood donors since 1993, which is consistent with culling of seropositive donors and a birth cohort effect. We found a novel association between HCV infection prevalence and gravidity that will be important to replicate in other US studies because of the public health implications regarding potential iatrogenic transmission in the obstetric setting. Finally, our intriguing results regarding an inverse association of obesity with both HCV infection and viremia may influence the direction of future research on the genetics and metabolic effects of chronic HCV infection, particularly among healthier HCV carriers, as opposed to those with preexisting liver disease.

**REASMINUS EPIDEMIOLOGY DONOR STUDY II**

Centers of the Pacific: E. L. Murphy (University of California San Francisco and Blood Systems Research Institute); M. P. Busch and B. Custer (Blood Systems Research Institute); and N. Hirschler (Blood Centers of the Pacific). The Institute for Transfusion Medicine: D. Triulzi, R. Kakaiya, and J. Kiss. Blood Center of Wisconsin: J. Gottschall and A. Mast.


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