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# Distribution of hepatitis A antibodies in United States blood donors

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## Abstract

**Background:** Recently, there has been an increase in the number of hepatitis A outbreaks in the United States. Although the presence of HAV RNA in blood donors is known to be very low, HAV antibody prevalence in this population is unknown.

**Methods:** Samples from 5001 US blood donors collected primarily in the Midwestern US in 2015 were tested for the presence of HAV IgG antibodies using chemiluminescent microparticles immunoassays on the ARCHITECT platform (Abbott Laboratories).

**Results:** The overall prevalence of IgG anti-HAV was 60%. Only one specimen was IgM anti-HAV positive for an incidence of 0.02%. IgG anti-HAV prevalence among donors 16 to 19 years was 67%, dropped to 54% among donors aged 40 to 49 years and increased to 70% among donors aged 80 to 93 years. No differences were seen by sex with overall IgG anti-HAV prevalence of 61% and 60% for males and females, respectively. Among the five states (Illinois, Indiana, Kansas, Kentucky, and Missouri) with the highest number of donors tested, IgG anti-HAV prevalence in Missouri (65%) was significantly higher ($P$<0.01) than that in Illinois (52%) or Kentucky (59%). No other significant differences between states were noted.

**Conclusions:** This study demonstrates the overall high rates of IgG anti-HAV in US blood donors with the low associated risk of HAV transfusion transmission is likely the result of low incidence and effective vaccination.

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## Introduction

Hepatitis A is a self-limiting liver disease caused by the hepatitis A virus (HAV), which is a member of the genus *Hepatovirus* in the family *Picornaviridae*. The virus is transmitted through the fecal-oral route following consumption of contaminated food and water, or contact with an infected individual. HAV infection is asymptomatic in about 70% of children younger than six years of age, but 70% of adolescents and adults develop symptoms[1].

In the United States from 1988 to 1991, 33% of the population had serological evidence of prior HAV infection based on data from the Third National Health and Nutrition examination Survey (NHANES-III). Anti-HAV prevalence was directly related to age rising from 10% in children less than 10 years of age to 75% in adults over the age of 70 years[2]. Further testing of NHANES specimens found a decrease in HAV seroprevalence in adults ≥20 years old from 29.5% during 1996–2006 to 24.2% during 2007–2012[3].

During 1995–1996, effective hepatitis A vaccines were licensed for use among persons ≥2 years of age. In 1966, the Advisory Committee on Immunization Practices (ACIP) recommended vaccinating persons in groups shown to be at high risk of infection and children living in communities with high rates of disease[2]. In 1999, the ACIP recommended vaccinating children living in states, counties, and communities in which hepatitis A rates were consistently above the national average[4]. A report from the U.S. Centers for Disease Control and Prevention (CDC) in 2016 indicated that the ACIP recommendation for childhood hepatitis A vaccination had resulted in increased population protection among children, but the proportion of adults with seroprotection had decreased[5].

Transfusion transmission of HAV is extremely rare due to the short duration of viremia during acute HAV infection (~10–50 days), the absence of a chronic carrier state, low incidence in the U.S. population, and the availability of an effective vaccine [6]. However, there is the potential of HAV transmission by clotting factor concentrates, particularly because the virus is not enveloped and very resistant to inactivation [6]. Thus, U.S. blood centers that provide plasma for further manufacture perform HAV nucleic acid screening either themselves or by their contract fractionator. Such testing is considered “in-process” with results not generated in time to interdict products for transfusion or to notify, defer and counsel donors of their test results[6]. The rationale for this was based on the rarity of transfusion transmission, high rate of asymptomatic resolving infection in healthy individuals, and the fact that due to the short duration of viremia, notification would occur only after infection has resolved. With the availability of real-time, automated testing platforms for HAV and parvovirus B19 by the two manufacturers of nucleic acid tests used in the U.S., reexamination of policies especially in the face of an increasing number of reported outbreaks either from contaminated food in single-sourced community outbreaks or on-going person-to-person outbreaks for which a source has not been identified may be warranted[7–9].

Although the prevalence of HAV RNA in blood donors is known to be very low, HAV antibody prevalence in this population is unknown. Thus, using a convenience sample available, anti-HAV prevalence was investigated.

## Methods

### Sample selection and preparation

Residual samples from blood donations made to the American Red Cross (ARC) from March 22 to April 3, 2015 were obtained. Samples from donations having reactivity to routine disease markers (e.g., hepatitis B virus, hepatitis C virus and human immunodeficiency virus) were excluded. Approximately 5000 samples were selected randomly from approximately 50,000 samples previously screened by research-use only HEV RNA assays for a study of HEV antibody prevalence[10,11]. A total of 5001 samples with adequate volume for testing were selected representing residents of 22 states. Blood was collected in plasma preparation tubes; the plasma from these tubes was stored at −70°C until tested[11]. Epidemiological data collected and provided with the specimens included the donor's age, sex, state of residence, and state where the donation was made. The samples were anonymized and sent to CDC for testing.

Informed consent was obtained from all donors in this study. As part of providing consent for blood donation, all donors are informed that their surplus screening samples may be used for studies on blood safety including those involving transfusion-transmissible infections. This HAV antibody prevalence study was approved by the ARC Institutional Review Board.

### Serological testing

Samples were tested for IgM anti-HAV (anti-HAV M, list number 06L2125) and IgG anti-HAV (anti-HAV G, list number 06L2725) using the automated chemiluminescent microparticle immunoassays (CMIA) on the ARCHITECT platform (Abbott Laboratories, Abbott Park IL). Reagents were provided from Abbott Laboratories as part of an investigator-initiated study. In the IgM anti-HAV assay any signal-to-cutoff (S/CO) value within 20% of the cutoff is considered a gray-zone result; the IgG anti-HAV assay does not have a gray-zone. For samples that fell in the IgM gray-zone, IgM anti-HAV reactivity was further evaluated using the IgM anti-HAV chemiluminescent immunoassay (CIA) (680 1812) on the Vitros ECi automated platform (Ortho Clinical Diagnostics, Rochester NY). Samples reactive by both IgM assays were considered confirmed positive. All testing was done according to manufacturers' instructions. IgM confirmed-positive samples were also tested for HAV RNA by an in-house nested PCR assay as previously described [12]

### Statistics

All statistical calculations and graphic visualizations were done in R (Ver 3.4.0)[13]. Two-sided Fisher's exact test for count data and non-parametric local regression (loess) were carried out in base R.

## Results

Of the 5001 samples tested, 3019 (60%) were positive for IgG anti-HAV. Remaining sample volume following IgG testing was available for further IgM anti-HAV testing for 4991 samples. Of these, all samples were IgM anti-HAV non-reactive except one sample that was in the gray-zone. The gray-zone sample was tested on an alternate assay (Vitros ECi) and

was IgM positive for an IgM incidence of 0.02%. HAV RNA was undetectable in this sample. Figure 1 shows the age distribution of the donors in this study.

An analysis of IgG anti-HAV prevalence by age showed that IgG anti-HAV prevalence among donors aged 16 to 19 years old was 67%, dropped to 54% among donors aged 40 to 49 years old and then increased to 70% among donors aged 80 to 93 years old (Figure 2). There are statistically significant differences between the prevalence rates for the donors 40 to 49 years of age versus either the donors 16 to 24, or 70 to 74 years of age ($P < 0.05$, two-sided Fisher's exact test). The percentage of IgG anti-HAV tested donors by sex was 53% male (n=2662) and 47% female (n=2339).

Among the five states (Illinois, Indiana, Kansas, Kentucky, and Missouri) with the highest number of donors based on donor residential zip code, the overall IgG anti-HAV prevalence among males and female donors was 61% and 60%, respectively and ranged from 50–67% (Table 1). Donors from the remaining states were not included in this analysis because none of these states had more than 8 donors. Although some significant differences in overall prevalence among the five states were observed, there was little overall variability (52% for IL to 65% for MO). An examination of IgG anti-HAV by age and sex showed that there was no difference between male and female donors, with the exception of the 40–44 year group ($P <0.0001$, Fisher's exact test, two-tailed, odds ratio = 3.0 (95% CI, 1.7 – 5.2)), with 70% of males (n=136) and 44% of females (n=118) testing IgG anti-HAV positive.

## Discussion

The overall prevalence for IgG anti-HAV among a population of blood donors predominantly from the Midwest is 60%. This is higher than the 33% rate seen for individuals tested from 1988 to 1991 using NHANES III samples[2]. The rate in adults ≥20 years old was 24% (total anti-HAV) in NHANES samples collected between 2007 and 2012[3]. There are several differences between these two populations. NHANES collects blood from healthy individuals ≥5 years of age and older, the United States donor population is restricted to individuals screened for risk behavior and who are ≥16 years of age. NHANES samples were collected from across the country using sampling methodology meant to be representative of the nation, while the studied blood donor population was not representative of the entire US and was predominantly from the Midwest. The (1988–1991) NHANES population is a pre-vaccination population while the current 2015 blood donor population and the (2007–2012) NHANES populations were sampled at least 11 years after the licensure of HAV vaccines, some in combination with hepatitis B vaccines (e.g., Twinrix; Glaxo Smith Kline, May 2001), thus likely increasing their penetrance in the population at large. The most likely explanation for the prevalence curve seen in Figure 2 is that younger donors have been vaccinated as a result of the ACIP recommendations[5], as mentioned in Klevens et al.[3] Prevalence then decreases in older donors up to those from 40 to 49 years of age due to the lack of concerted vaccination programs for older children and adults. After this point donors in the population >49 years of age have an increase in IgG anti-HAV due to natural infection as was seen in the NHANES study. We were not able to test these specimens to resolve the issue of IgG prevalence resulting from vaccination versus natural immunity after infection.

Among the five states with the highest numbers of donors, only the IgG anti-HAV prevalence in Missouri (65%) was significantly higher than the prevalence in Illinois (52%) and Kentucky (59%) (Table 1, $P<0.01$). The only difference in IgG anti-HAV prevalence between males and females was in the 40–44-year age range ($P<0.0001$).The blood donor population used in this study did not represent the entire United States and was restricted mainly to the Midwest. In addition, blood donors generally represent a low-risk population regarding drug use and sexual behaviors, and include many young individuals who would have the opportunity to be vaccinated and thus differ from the general US population[14]. Another limitation to this study is that not all samples were tested for HAV RNA; however, its frequency in blood donors is extremely low (on the order of less than 1 per 2 million donors tested annually; ARC internal data).

In summary, this study demonstrates overall high background rates of IgG anti-HAV in the general blood donor population particularly in younger aged, presumably vaccinated donors, and those over 60 years old. The presence of antibody in 60% of the donor population undoubtedly affords protection from infection in an HAV-exposed recipient[15]. The low risk of HAV transfusion transmission was further demonstrated by the absence of acute HAV infection identified in this dataset and low rate of recent infection as measured by IgM anti-HAV (estimated at 2 per 10,000 from the single IgM anti-HAV-confirmed-positive sample). All of these findings further confirm the low transfusion transmission risk of HAV in the United States.

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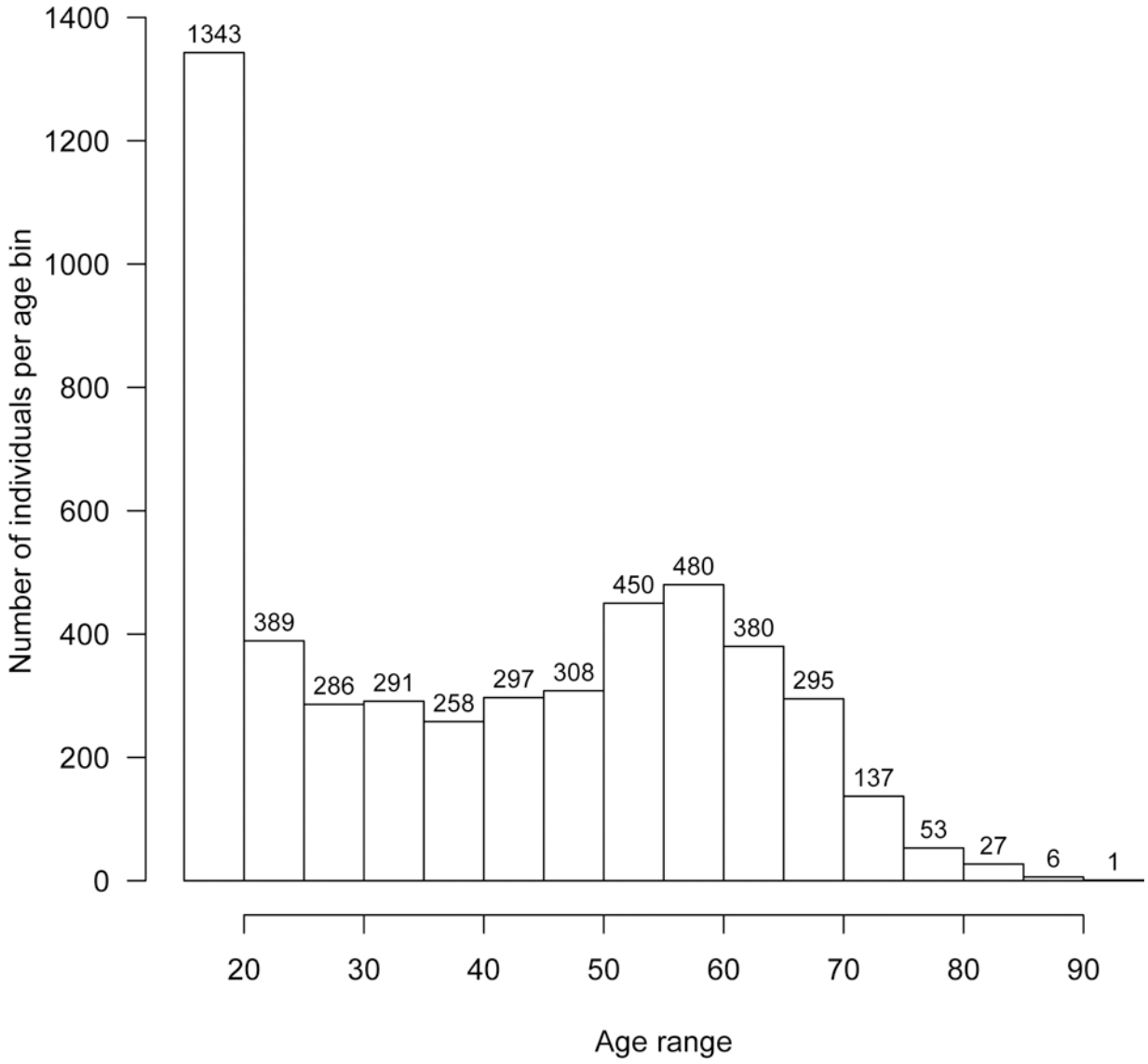


**Figure 1.**

Age distribution for participants (n=5001). The number of participants were grouped into 5 year age bins except for the youngest age group, which covered individuals from 16 to 19 years of age, inclusive, and the oldest age group, which included individuals from 90 to 93 years of age, inclusive. The numbers at the top of each bar are the number of individuals in that age range.

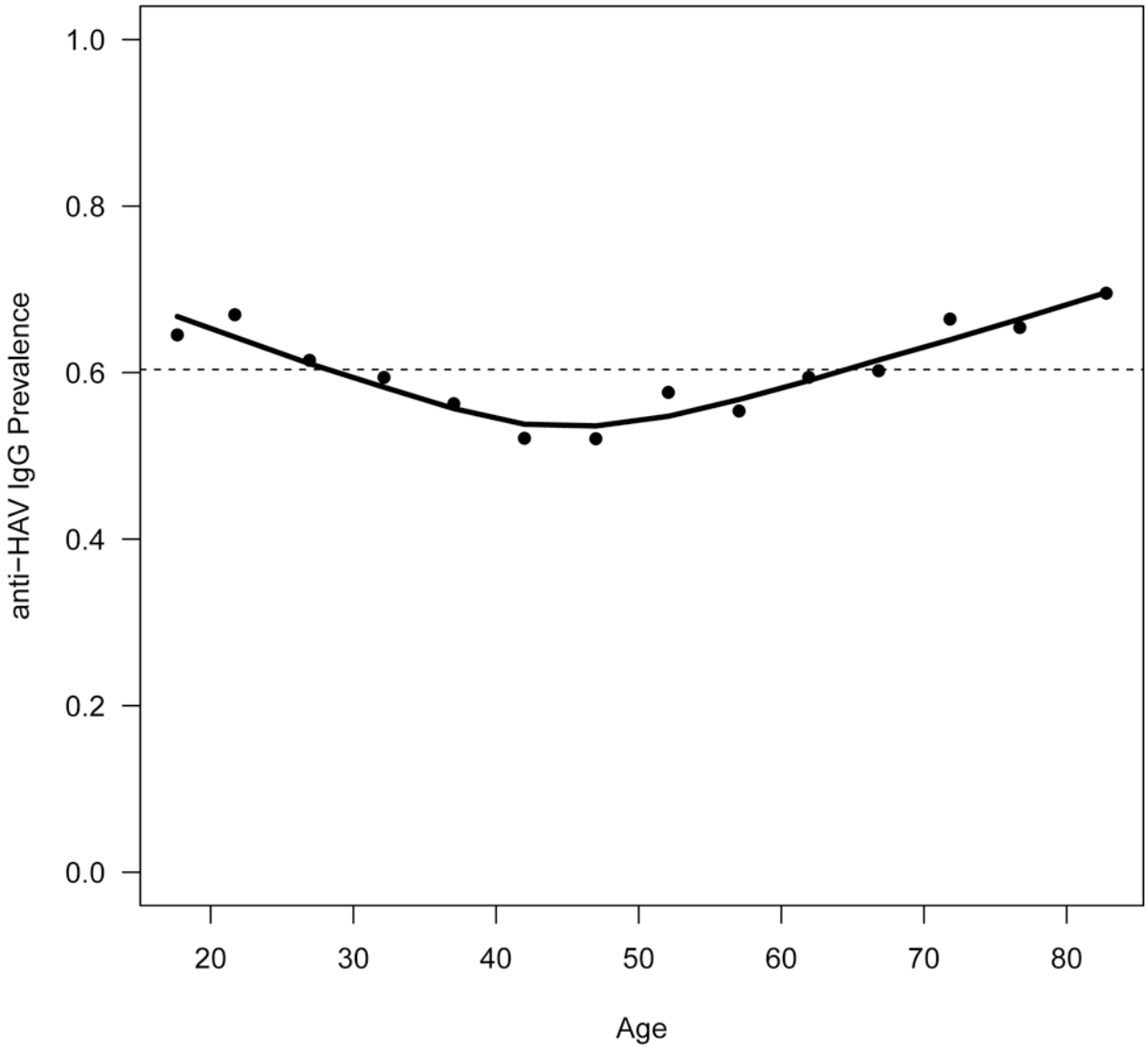


**Figure 2.**

IgG anti-HAV prevalence by age (n=5001). The fractional IgG anti-HAV reactivity by age range bin is plotted against the mean age within each age bin. Each bin covers 5 years of age except for the first bin, which covered individuals from 16 to 19 years of age, inclusive, and the oldest age group, which included individuals from 80 to 93 years of age, inclusive. The solid black line is the non-parametric local regression line for the data calculated with the loess function in R. The horizontal dashed line is the mean fractional IgG anti-HAV reactivity among all individuals tested.

**Table 1.**

The five states with the highest number of donors were compared (n=4960 from 5 states) with the fraction of IgG antibody reactive donors by state and sex shown. All states show the data for all states with donors (n=5001).

| | Population | | |
|---|---|---|---|
| **State** | **All** | **Female** | **Male** |
| IL | 0.52* | 0.50 | 0.54 |
| IN | 0.60 | 0.61 | 0.59 |
| KS | 0.61 | 0.67 | 0.53 |
| KY | 0.59* | 0.60 | 0.57 |
| MO | 0.65 | 0.62 | 0.67 |
| All states | 0.60 | 0.60 | 0.61 |

* $P < 0.01$ (vs. Missouri, Fisher's exact test for count data and confidence intervals do not overlap).